An Assessment of World Health Organization Criteria for Severe Acute Respiratory Syndrome in Patients with Cancer

Jin Gu, M.D.1
Aiwen Wu, M.D.1
Jiyou Li, M.D.2
Xiaopeng Zhang, M.D.3
Jian Fang, M.D.4
Ming Li, M.D.1
Yunfeng Yao, M.D.1
Yang Ke, Ph.D.5
Jiang Gu, Ph.D.6
Mingzhe Chen, M.D.7
Weicheng You, M.D.8

1 Department of Surgical Oncology, School of Oncology, Peking University, Beijing, People’s Republic of China.
2 Department of Pathology, School of Oncology, Peking University, Beijing, People’s Republic of China.
3 Department of Radiology, School of Oncology, Peking University, Beijing, People’s Republic of China.
4 Department of Medicine, School of Oncology, Peking University, Beijing, People’s Republic of China.
5 Department of Genetics, School of Oncology, Peking University, Beijing, People’s Republic of China.
6 Department of Pathology, Healthcare Center, Peking University, Beijing, People’s Republic of China.
7 Department of Cardiology, Third Hospital, Peking University, People’s Republic of China.
8 Department of Epidemiology, School of Oncology, Peking University, People’s Republic of China.

BACKGROUND. The differential diagnosis of severe acute respiratory syndrome (SARS) in patients with cancer can be challenging. Although diagnostic criteria for SARS have been issued by the World Health Organization (WHO), simple adoption of the established criteria may lead to overdiagnosis in patients with cancer or to an increase in the risk of spreading SARS within cancer hospitals.

METHODS. The authors report their experience with the exclusion and quarantine of patients with cancer during the peak of the SARS epidemic in Beijing, China. The patients included 4 males and 7 females with a median age of 66 years (range, 39–73 years).

RESULTS. All 11 patients met the WHO diagnostic criteria for probable SARS. Among those 11 patients with probable SARS, only 1 had confirmed SARS; for the other 10 patients, the possibility of SARS infection was ruled out.

CONCLUSIONS. Special attention must be paid to patients with cancer who have symptoms similar to those seen in SARS. Although the WHO diagnostic criteria for SARS should be widely accepted, they are not definite or practical in certain populations. Cancer 2004;100:1374–8.

© 2004 American Cancer Society.

KEYWORDS: SARS, differential diagnosis, quarantine, cancer patients, neoplasma.

Severe acute respiratory syndrome (SARS) is a highly infectious disease. Its clinical manifestations include fever, progressive pulmonary infiltration, lymphopenia, and in severe cases, respiratory failure.1,2 SARS outbreaks have swept quickly through many regions in the world, particularly East Asia.3 The number of patients with newly diagnosed SARS exceeded 5000 in Mainland China and reached 2490 in Beijing by May 24, 2003.4

Patients with compromised immune function, such as those age > 60 years and those with other severe chronic conditions, had a poor prognosis and high fatality rates.5 Most patients with cancer had poor immune function and were vulnerable to infections that could present with fever, an important manifestation of SARS. The differential diagnosis of SARS in patients with cancer sometimes was challenging. Although definitions of SARS were issued by the World Health Organization (WHO), simple adoption of the established criteria could lead to overdiagnosis in patients with cancer or to an increase in the risk of spreading SARS within cancer hospitals. Therefore, special attention should be paid to patients with cancer in the diagnosis of SARS.
MATERIALS AND METHODS

In the current report, we present our experience with exclusion and quarantine for SARS in patients with cancer during the peak of the SARS epidemic in Beijing, China. Clinical definitions of SARS issued by WHO were used. Exclusion and quarantine procedures were performed for patients with a body temperature ≥ 38 °C, ≥ 1 clinical finding of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, hypoxia), and radiographic evidence of pneumonia or respiratory distress syndrome. Eleven inpatients with cancer who were admitted to Peking University School of Oncology (Beijing, China) and who recently developed fever and other respiratory symptoms similar to those seen in SARS were enrolled in the current study. These patients included 4 males and 7 females with median age of 66 years (range, 39–73 years). All 11 patients met the WHO diagnostic criteria for probable SARS. Among the 11 patients with cancer and probable SARS, only 1 had confirmed SARS; for the other 10 patients, the possibility of SARS infection was ruled out.

RESULTS

The patient with confirmed SARS was a woman age 45 years. The patient underwent a left mastectomy 16 months earlier and was readmitted for disease recurrence in the liver, bone, and distal lymph nodes. She began to receive chemotherapy (vinorelbine 40 mg intravenously on Days 1 and 8 and cisplatin 40 mg intravenously on Days 2 and 8) on May 8, 2003. The patient had a sudden onset of fever (38.3 °C) with shivering the next day. No coughing, headache, myalgia, rigor, nausea, or emesis was present, and no rales were detected. The patient’s blood test showed a white blood cell (WBC) count of 3.9 × 10^9/L, a neutrophil (GR) % of 90%, a lymphocyte (LN) % of 9%, and a platelet (PLT) count of 92 × 10^9/L. A chest X-ray showed lower right lung infiltrates (Fig. 1). Ofloxacin (200 mg intravenously) was administered twice daily. The fever continued the next day, and a blood test showed a WBC count of 4.4 × 10^9/L, a GR% of 81.2%, a LN% of 17.1%, and a PLT count of 60 × 10^9/L. A chest X-ray showed that the infiltrates in the lower right lung had enlarged significantly (Fig. 1). Infection with the SARS virus was then suspected, despite the patient’s denial of close contact with any patient with SARS. Specialists from Peking University First Hospital were consulted, and the diagnosis of SARS was confirmed. The patient was transferred to a specialized SARS hospital and was treated accordingly.

General information on the 10 patients with probable SARS is shown in Table 1. There were 4 male patients and 6 female patients with median age of 66.5 years (range, 39–73 years). Nine patients had received multiple courses of adjuvant or salvage chemotherapy and/or radiotherapy. Eighty-two percent of patients had a body temperature > 38 °C. More than 50% of patients presented with symptoms such as dyspnea, cough, headache, and myalgia, among others. WBC counts were normal or decreased in 70% of patients. Three patients and 5 patients developed lymphopenia (< 1.0 × 10^9/L) and neutropenia (< 3.5 × 10^9/L), respectively. Elevated aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase levels were found in five patients, two patients, and four patients, respectively. In addition, there was radiographic evidence of infiltrates in the lungs consistent with pneumonia.

Most patients met the diagnostic criteria for probable SARS. Information on the 11 patients was pre-
sented to a SARS panel composed of experts from the Departments of Medicine, Surgery, and Radiotherapy, as well as other departments. After disease and contact history inquiry and chest X-ray review, experimental therapies directed against common pulmonary bacterial infections were recommended. The clinical outcomes of the 10 patients with cancer and probable SARS after short-term antibiotic therapy are summarized in Table 2.

The possibility of SARS was ruled out for three patients (Patients 1, 5, and 8) based on their histories and the results of experimental antibiotic therapies. Patient 1 developed a high fever (39 °C) with headache and myalgia 3 days after receiving chemoemboliza-

---

### Table 1

| Patient no. | Gender | Age (yrs) | Diagnosis | Department | Duration of illness (mos) | Treatment | Karnofsky score | Accompanying disease |
|-------------|--------|-----------|-----------|------------|--------------------------|-----------|----------------|---------------------|
| 1           | F      | 39        | Postoperative islet cell tumor; liver metastasis | Interventional therapy | 60.0 | Surgery (interventional) and/or CT | 50 | None |
| 2           | F      | 47        | Right breast CA; hysteromyoma | Surgery | 1.0 | Surgery | 80 | None |
| 3           | M      | 56        | Tumor of left adrenal gland | Surgery | 0.5 | Intent to perform surgery | 90 | None |
| 4           | F      | 56        | Postoperative breast CA, multiple metastases of liver, peritoneal cavity, and pleura | Surgery | 102.0 | Surgery, CT, hormone therapy, immunotherapy | 30 | None |
| 5           | F      | 66        | Endometrial CA, breast CA, and laryngeal CA | Radiotherapy | 42.0 | Surgery, CT, RT, immunotherapy | 50 | Allergy |
| 6           | M      | 67        | Postoperative malignant mixed tumor on right cheek and soft palate; multiple metastasis of cervical lymph nodes, chest wall, and bone | Traditional Chinese medicine | 216.0 | Surgery, CT, RT, traditional Chinese medicine, immunotherapy | 60 | None |
| 7           | M      | 67        | Left lung CA | Internal medicine | 3.0 | CT, RT | 50 | None |
| 8           | F      | 69        | Primary hepatic CA | Internal medicine | 22.0 | Interventional chemoembolization, systemic CT | 60 | Cirrhosis, CHD and chronic cystitis, cerebral infarction |
| 9           | M      | 70        | Metastatic liver CA (unknown primary site) | Intervventional therapy | 4.0 | Immunotherapy | 60 | Chronic bronchitis |
| 10          | F      | 73        | Left lung CA | Internal medicine | 8.0 | CT | 70 | CHD, chronic bronchitis |

F: female; M: male; CA: carcinoma; CT: chemotherapy; RT: radiotherapy; CHD: coronary heart disease.

---

### Table 2

| Patient no. | Body temperature | Absolute WBC count | Absolute lymphocyte count | Absolute platelet count | Chest X-ray | Interval (days) |
|-------------|------------------|---------------------|---------------------------|-------------------------|-------------|----------------|
| 1           | Decreased        | Decreased           | Decreased                 | Increased               | No obvious change | 2              |
| 2           | Decreased        | Increased           | Decreased                 | Decreased               | Infiltrates enlarged on the second day and absorbed on the third day | 4              |
| 3           | Decreased        | NA                  | NA                        | NA                      | Absorption   | 16             |
| 4           | Decreased        | Increased           | Increased                 | Decreased               | No apparent change | 1              |
| 5           | Decreased        | Increased           | Increased                 | Increased               | Absorbed     | 2              |
| 6           | Decreased        | Decreased           | Increased                 | Decreased               | Decreased    | 2              |
| 7           | Decreased        | Decreased           | Decreased                 | Increased               | Improved on the second day, no further change on the third day | 2              |
| 8           | Decreased        | Decreased           | Increased                 | Increased               | Decreased    | 2              |
| 9           | Decreased        | NA                  | NA                        | NA                      | Decreased    | 2              |
| 10          | Decreased        | NA                  | NA                        | NA                      | No apparent change | 2              |

WBC: white blood cell; NA: not available.
tion. However, the patient presented with the same signs and symptoms previously during chemoembolization. This indicated a febrile reaction to tumor necrosis. Patient 5 had a sudden onset of rigor and fever 1 hour after receiving a thymosin transfusion. Although bilateral lung infiltrates with ill-defined borders were found in the chest X-ray, the diagnosis favored an allergic reaction. Patient 8 was a female patient with primary hepatic malignancy. Her absolute neutrophil count was only $0.5 \times 10^9/L$ at that time, and she had developed fever $>38^\circ C$ on several occasions in the preceding 6 months. Her body temperature would decrease after she received prophylactic antibiotics and agents that increased leucocyte counts. Thus, febrile neutropenia was suspected. SARS was ruled out for the other seven patients due to their positive responses to experimental antibiotics. In these seven patients, body temperature decreased, and pulmonary lesions were absorbed. Two of these seven patients (Patients 7 and 10) had lung carcinoma and presented with dyspnea and fever. The possibility of SARS was finally ruled out for one patient (Patient 2) after she began receiving superbroad-spectrum antibiotics and exhibited favorable signs 4 days later (Fig. 2).

**DISCUSSION**

The current series showed that most patients with cancer received chemotherapy and/or radiotherapy, which compromised host immune function to an even greater extent. Patients could not respond to an attack by the SARS virus in the same way that healthy individuals could. The clinical manifestation of SARS in patients with cancer may be atypical. Moreover, the increased possibility of infection in patients with cancer paralleled the decline in neutrophil counts and increased significantly when the number of neutrophils in the peripheral blood decreased to $1 \times 10^9/L$. Both situations made the differential diagnosis of SARS in patients with cancer difficult. In addition, patients sometimes denied their contact history during the peak of the SARS epidemic; this exacerbated the difficulty of diagnosing SARS and rendered the epidemiologic evidence for the WHO case definitions unreliable.

Based on our experience, we recommend the following steps to improve the accuracy of diagnosis: 1) clinical data related to fever should be collected and reviewed carefully, and a consultant panel should be organized that includes experts from internal medicine, clinical oncology, surgery, and medical radiology departments in cancer hospitals; 2) attention should be paid to differential diagnoses between primary diseases (such as lung cancer) and diseases caused by other factors, even if symptomatic, laboratory, and radiographic findings are consistent with SARS; 3) radiographic manifestations should be reviewed carefully, with special attention paid to possible causes other than SARS and to radiographic changes following experimental therapy; 4) experimental therapies should begin early and should be adjusted in a timely fashion, and clinical and radiographic presentation should be followed closely; and 5) most importantly, quarantine and close surveillance should be performed once SARS is suspected. Medical professionals should take effective protection measures in their work.

In conclusion, special attention must be paid to patients with cancer who have symptoms similar to those seen in SARS. Although the WHO diagnostic criteria for SARS should be widely accepted, they are not definite or practical in certain populations. The keys to achieving an accurate diagnosis are detailed
inquiry regarding history and close follow-up of the effects of experimental antibiotic therapy. Diagnostic methods directed at specific pathogens may be helpful in the future.9

REFERENCES
1. [No authors listed.] Preliminary clinical description of severe acute respiratory syndrome. MMWR Morb Mortal Wkly Rep. 2003;52:255–256.
2. Centers for Disease Control and Prevention. Updated interim U.S. case definition for severe acute respiratory syndrome (SARS) [monograph online]. Available from URL: http://www.cdc.gov/ncidod/sars/casedefinition.htm [Accessed 11 October 2003].
3. Centers for Disease Control SARS Investigative Team. Outbreak of severe acute respiratory syndrome—worldwide, 2003. MMWR Morb Mortal Wkly Rep. 2003;52:226–228.
4. World Health Organization. China daily report of SARS cases [monograph online]. Available from URL: http://www.who.int/csr/sars/china2003_05_24.pdf [Accessed 11 October 2003].
5. Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agents of severe acute respiratory syndrome in Hong Kong. Lancet. 2003;361:1761–1766.
6. Yang M, Hon KL, Li K, Fok TF, Li CK. The effect of SARS coronavirus on blood system: its clinical findings and the pathophysiologic hypothesis. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2003;11:217–221.
7. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med. 2003;348:1953–1966.
8. Hughes WT, Armstrong D, Bodey GP, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Infect Dis. 1990;161:381–396.
9. Nie QH, Luo XD, Hui WL. Advances in clinical diagnosis and treatment of severe acute respiratory syndrome. World J Gastroenterol. 2003;9:1139–1143.