Original Article

Measles Outbreak in Pediatric Hematology and Oncology Patients in Shanghai, 2015

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Abstract

Background: Despite substantial progress toward measles control are making in China, measles outbreaks in immunocompromised population still pose a challenge to interrupt endemic transmission. This study aimed to investigate the features of measles in pediatric hematology and oncology patients and explore the reasons behind the outbreak.

Methods: We collected demographic, epidemiological, and clinical data of immunocompromised measles children. All suspected measles cases were laboratory-confirmed based on the presence of measles IgM and/or identification of measles RNA. The clinical data were statistically analyzed by *t*-test for continuous variables and Fisher's exact test for categorical variables.

Results: From March 9 to July 25 in 2015, a total of 23 children with malignancies and post hematopoietic stem cell transplantation (post-HSCT) were notified to develop measles in Shanghai. Of these 23 patients with the median age of 5.5 years (range: 11 months–14 years), 20 (87.0%) had received 1–3 doses of measles vaccine previously; all patients had fever with the median fever duration of 8 days; 21 (91.3%) had cough; 18 (78.3%) had rash; 13 (56.5%) had Koplik's spot; 13 (56.5%) had complications including pneumonia and acute liver failure; and five (21.7%) vaccinated patients died from severe pneumonia or acute liver failure. Except the first patient, all patients had hospital visits within 7–21 days before measles onset and 20 patients were likely to be exposed to each other.

Conclusions: The outcome of measles outbreak in previously vaccinated oncology and post-HSCT pediatric patients during chemotherapy and immunosuppressant medication was severe. Complete loss of protective immunity induced by measles vaccine during chemotherapy was the potential reason. Improved infection control practice was critical for the prevention of measles in malignancy patients and transplant recipients.

Key words: Children; Measles; Oncology; Vaccination

Introduction

Measles is a highly contagious, serious disease and can be spread by direct contact, droplets, or airborne transmission. Global measles control and prevention have been very successful since the introduction of measles vaccination in 1960s. Despite the availability of a safe and effective vaccine, measles remains one of the leading causes of vaccine-preventable death among young children globally.[1] The average annual measles incidence in China reduced dramatically from 572.0/100,000 during 1960s to 7.6/100,000 during 1990s.[2] Since 2000, measles resurged in China, and the average reported measles incidence reached as high as 9.4/100,000 in 2005, which is probably due to the massive rural to urban immigration, incomplete or missed measles vaccination in migrant children and in the resource-limited areas. Attenuated-live measles vaccine was introduced into China in 1965, and the first dose of measles vaccine is recommended to be administered to infant at the age of 8 months. Thus, China changed the timing of the second dose measles vaccine from 7 years to 18–24 months in 2005 based on the epidemiological surveillance data and strengthened catch-up measles vaccination among migrant children.[3] Although the number and annual incidence of

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measles decreased to nadir (6183; 0.46/100,000) in 2012 after the nationwide campaign of Supplementary Immunization Activities in 2010, the outbreak of measles re-emerged in China in recent years, with 27,646, 52,628, and 44,939 measles cases reported in 2013, 2014, and 2015, respectively.[4,5] Shanghai is an economically developed region with a high population density in China. In fact, the coverage of two-dose childhood measles immunization has reached >95% in local Shanghai children since the middle 1980s.

In early 2015, the reported number of measles cases exceeded that of the same periods in 2013–2014 in both the whole country and Shanghai.[6] Unexpectedly, measles outbreak occurred in immunocompromised children in the hospital setting during the peak months of measles outbreak in 2015 in Shanghai. In this study, we described the epidemiological features, clinical manifestation, and outcome of 23 children with malignancies and post hematopoietic stem cell transplantation (post-HSCT).

Methods

Patients and definition of measles case

All 23 measles children with malignancies and post-HSCT were treated in the infectious disease unit of Children's Hospital of Fudan University, Shanghai (hospital A), which was the largest tertiary teaching pediatric medical center in Shanghai and was the only assigned referral hospital to manage childhood notifiable infectious diseases. Measles case was diagnosed based on both clinical manifestations and laboratory confirmation with the presence of measles-specific IgM in serum and/or measles virus RNA positive in throat swab.

Laboratory investigations

For all patients, the throat swabs and serum samples were collected at the time of admission and these samples were delivered to the measles reference laboratory of Shanghai Center for Disease Control and Prevention (CDC). IgM antibody against measles virus was tested by enzyme-linked immunosorbent assays (ELISA), and measles virus RNA was tested by reverse transcription-polymerase chain reaction (RT-PCR). If the first serum sample was negative for anti-measles virus IgM antibody, a second serum sample was routinely collected 7–10 days after illness onset.

A commercial one-step real-time RT-PCR kit (Jiangsu Bioperfectus Technologies Co., Ltd., Suzhou, China) was used to detect measles virus in the swab samples in the CDC laboratory. A specimen was considered positive for measles virus if reaction growth curves cross the threshold line within 36.6 cycles, according to the manufacture's instruction. Anti-measles IgM was detected using an IgM μ-chain capture ELISA (Zhuhai Haitai Biological Pharmacy Enterprise Co., Ltd., Zhuhai, China) following the manufacturer's instruction. The optical density (*A*) was read at a wavelength of 450 nm. The test was valid if the *A* value for the negative control was 0.00–0.15 and the *A* value for the positive control was 0.30–1.80. Anti-measles IgM level was calculated as the ratio of the *A* value obtained from the test sample to the *A* value obtained from the negative control determined concurrently, and the ratio value ≥2.1 was determined as a positive result.

Furthermore, each patient received a comprehensive laboratory investigation including complete peripheral blood cell count, C-reactive protein (CRP), procalcitonin (PCT), serum biochemical tests, blood culture, bacteria culture, and antigen test of respiratory pathogens of nasopharyngeal aspirate or sputum (immunofluorescence antibody assay for testing respiratory viruses and PCR for testing mycoplasma pneumonia), and chest X-ray. For patients experiencing prolonged fever or worsening of respiratory condition, serum 1,3-β-glucan and galactomannan were screened to detect possible invasive fungal infection.

Data collection

Data collection was based on the medical record during hospitalization, and data analysis was performed anonymously. We routinely collected demographic features, vaccination status, possible exposure to measles patients within 7–21 days before onset of illness, clinical symptoms and signs, laboratory findings, complications, treatment regimens, and prognosis according to the records of medical charts.

Pneumonia was diagnosed based on both respiratory symptoms (cough, dyspnea, or moist rales on auscultation) and chest X-ray images; acute liver failure was defined based on the diagnostic criteria.[7] Leukopenia was diagnosed when the count of white blood cell (WBC) was $<4.0 \times 10^9$/L. Neutropenia was diagnosed when the absolute neutrophils count (ANC) of peripheral blood was $<0.5 \times 10^9$/L. The count of WBC shown in the text was the nadir count during measles.

Ethical approval

This was a retrospective study, and data analysis was performed anonymously. Therefore, this study was exempt from the ethical approval and informed consent from a parent.

Statistical analysis

Clinical data were analyzed with Stata 10.0 (StataCorp., College Station, Texas, USA). Fisher's exact test was used to compare the categorical variables between groups and *t*-test was used to compare continuous variable. A two-sided $P < 0.05$ was considered statistically significant.

Results

Epidemiological characteristics

From March 9 to July 25 in 2015, a total of 23 oncology children and posttransplant children were confirmed with measles in Shanghai with a median age of 5.5 years (range: 11 months–14 years). The first patient was a 15-month-old girl who was undergoing maintenance chemotherapy for malignant histiocytosis and did not receive measles vaccine since she developed malignancy at the age of 5 months. This girl visited the oncology clinic of

children's hospital B for persistent fever and cough between March 9 and March 16. Sixteen subsequent measles patients, who visited the same oncology clinic of the children's hospital B for the management of malignancy or febrile illness, developed measles-associated symptoms between March 14 and April 19. The 17 patients from hospital B had been possibly exposed to each other within 7–21 days before measles onset. The other six measles children with malignancy also visited the hospital for medical care 7–21 days before measles onset (among whom, five patients visited the hospital A, and one patient visited the children's hospital C). All the 23 patients were admitted or transferred to the isolation wards of hospital A when they were suspected or confirmed to be a measles case.

The hospitals B performed infection control measures and strengthened active screening of suspected measles case from March 21 to April 31, 2016, on the basis of febrile symptom after probable exposure when the first three measles cases from the same oncology center were confirmed. A total of 42 febrile suspected cases visiting the oncology center of Hospital B received active screening of measles through detection of measles-specific IgM in serum and measles virus RNA in throat swabs, and another 14 patients were laboratory-confirmed with measles. The hospital A and C performed infection control measures after the first suspected case occurred among oncology patients. All of the secondary measles patients did not receive timely intravenous immunoglobulins (IVIG) as passive immunization after suspected exposure.

Measles vaccination status

Measles vaccination status was available in 22 patients and unknown in one patient. There were two unvaccinated patients because they were diagnosed as malignancy before the age of 8 months and still received chemotherapy when they contracted measles. Among the 20 vaccinated children: 2 (2/22, 9.1%) had received three doses of measles vaccine, 13 (13/22, 59.1%) had received 2 doses of vaccine, and five (5/22, 22.7%) had received 1 dose of vaccine (the interval between vaccination and onset of measles was >6 months) [Table 1].

Clinical characteristics

All of the 23 (100.0%) patients had fever with the median fever duration of 8 days; 21 (91.3%) had cough; 18 (78.3%) had rash; 14 (60.9%) had conjunctivitis; 13 (56.5%) had Koplik's spot; and 5 (21.7%) had hoarseness. In a few of the patients, the appearance and sequence of rash were atypical. The types of underlying diseases included leukemia in 9 patients, lymphoma in five patients, neuroblastoma in three patients, myelodysplastic syndromes in two patients including one patient who had received HSCT, malignant histiocytosis in one patient, nephroblastoma in one patient, rhabdomyosarcoma in one patient, and aplastic anemia in one patient who had received HSCT. Twenty (87.0%) patients developed measles within 0–60.0 days after chemotherapy (mean: 9.4 ± 13.6 days; median: 4.0 days; "0" means ongoing chemotherapy or just completion of chemotherapy), and the remaining three patients did not receive chemotherapy during recent 3 months [Table 2].

Of the 23 patients, 22 (95.7%) were positive for measles-specific IgM antibody (negative in case 14) in serum and 22 (95.7%) were positive for measles virus RNA (negative in case 23) in throat swab; 14 (60.9%) patients had leukopenia, and three (13.0%) had neutropenia during the illness.

Treatment and outcomes

Of the 23 patients, 13 (56.5%) had complications including pneumonia in 12 (12/13, 92.3%), and acute liver failure in one (7.7%). Five (21.7%) patients required mechanical ventilation and four patients died. Twenty-one (91.3%) received IVIG (0.25–3.50 g/kg), 17 (73.9%) received antibiotics treatment for prolonged fever, persistently elevated CRP or PCT, and/or worsening pneumonia.

Characteristics of fatal cases

Five (21.7%) patients died, and all of them had been vaccinated against measles (three patients received two doses, and two patients received one dose previously). Among the five fatal patients, two patients received more prolonged and intensive chemotherapy for relapsed leukemia; the other three patients had received intensive chemotherapy within 30 days before measles attack. The median interval between measles onset and completion of chemotherapy was 4.0 days (range: 0–23 days) similar to that of survival cases. The median days of fever were 16.0 days (range: 12–23 days), significantly longer than that of survival cases (16.0 days vs. 6.5 days; $t = 2.42$, $P = 0.025$). The median days of hospitalization was 10.0 days (range: 3–26 days), significantly longer than that of survival cases (10.0 days vs. 5.0 days; $t = 2.15$; $P = 0.044$). Only one patient (case 2) had neutropenia, but ANC quickly recovered to the normal level after treatment. Five fatal cases showed significantly elevated CRP at the end of illness (>160 mg/L). All the fatal cases received a large dose of IVIG (1.0–3.5 g/kg) and broad-spectrum antibiotics, and four cases had mechanical supportive ventilation. Finally, the five patients died from severe pneumonia and acute liver failure.

Discussion

This study reported the measles outbreak in pediatric patients with malignancies and post-HSCT during the measles epidemic in China. The clinical features of measles in pediatric cancer patients and HSCT recipients were well illustrated in this study, which were atypical comparing with that of immunocompetent children. Surprisingly, these patients almost had breakthrough infection and were likely to contract measles during hospital visiting. This issue raised a public concern on both measles control in health-care setting and prevention of measles in high-risk susceptible immunocompromised patients.

The outcomes of this measles outbreak in malignancy children during chemotherapy and HSCT recipients were serious. Measles-related complications occurred in 56.5%

Table 1: Epidemiological features of measles in pediatric hematology and oncology patients in Shanghai, 2015

Case number*	Age (year)	Sex	Underlying disease	Hospital visits within 3 weeks before measles onset	Date of measles onset	Interval between measles onset and completion of chemotherapy (days)†	Doses of vaccination	Days of hospitalization
1	1	Female	MH	/	March 9	0	0	4
2	12	Male	Burkitt's lymphoma	Hospital B	March 14	0	2	7
3	5	Male	Lymphoma	Hospital B	March 15	0	2	4
4	10	Male	ALL (relapsed)	Hospital B	March 16	0	1	16
5	10	Female	ALL (relapsed)	Hospital B	March 20	15	2	3
6	11	Male	ALL (relapsed)	Hospital B	March 21	3	3	6
7	1	Male	ALL	Hospital B	March 24	9	1	3
8	2	Female	Lymphoma	Hospital B	March 29	4	2	4
9	9	Male	Leukemia	Hospital B	March 29	2	2	4
10	3	Female	Biclonal leukemia	Hospital B	March 29	0	1	4
11	5	Male	Nephroblastoma (relapsed)	Hospital B	March 30	15	2	6
12	14	Female	MDS (posttransplantation)	Hospital B	March 30	/	2	8
13	11Month	Male	Neuroblastoma	Hospital B	March 30	10	0	4
14	8	Male	ALL	Hospital B	April 2	5	2	7
15	1	Male	MDS	Hospital B	April 3	/	1	3
16	7	Female	Neuroblastoma	Hospital A	April 10	60	Unknown	7
17	13	Female	Aplastic anemia (posttransplantation)	Hospital B	April 12	/	2	9
18	2	Male	NHL	Hospital B	April 19	4	2	3
19	3	Female	Rhabdomyosarcoma	Hospital A	April 20	4	2	26
20	2	Female	Neuroblastoma	Hospital A	April 30	23	1	10
21	8	Female	T-cell lymphoma	Hospital C	April 30	7	2	22
22	3	Male	ALL	Hospital A	May 8	23	2	8
23	11	Female	ALL (relapsed)	Hospital A	July 25	4	3	10

*Sorted by the date of measles onset; †"0" means that patient developed measles during receiving chemotherapy; "/" means that patient did not receive chemotherapy at least 3 months recently. MH: Malignant histiocytosis; ALL: Acute lymphoblastic leukemia; MDS: Myelodysplastic syndrome; NHL: Non-Hodgkin's lymphoma; HSCT: Hematopoietic stem cell transplant.

of patients, and the case-fatality rate reached 21.7% in our serial patients. Previous literature reviews and case reports also reported severe complications and high morbidity for measles in immunocompromised patients and cancer children.[8-11] Of particular note, 20 (90.9%) of 22 patients had received 1–3 doses of measles vaccine before the diagnosis of underlying diseases, and the five fatal patients were all vaccinated previously, suggesting that breakthrough measles infection can be life-threatening in vaccinated immunocompromised children. Chemotherapy-induced immune suppression may result in significant loss of preexisting protective antibodies against vaccine antigens due to long-term impairment of humoral immunity in cancer patients, HSCT recipients, and other immunocompromised population.[12-16] Loss of protective serum antibody titers against measles after completion of chemotherapy was reported in 21–25% of cancer children.[12,13] However, the existing studies revealing the effect of chemotherapy-induced immune depression on dynamic change of protective serum antibodies against vaccine antigens in vaccinated oncology children were scarce. Our clinical data indirectly indicated the complete loss of protective humoral immunity induced by measles vaccine during chemotherapy.

Currently, it is recommended that cancer patients and HSCT recipients could be immunized or reimmunized at appropriate intervals to reduce the risk of vaccine-preventable infection.[15,17,18] Live vaccines administrations are usually contraindicated to cancer patients during chemotherapy and are recommended to be administered to cancer patients 3–6 months after cancer chemotherapy.[17,18] The panel of experts of the Italian Association Pediatric Hematology Oncology suggests vaccination for measles can be optional for pediatric patients during chemotherapy if the adequate $CD4^+$ immune recovery in case of epidemic, considering the high morbidity and the potential for mortality in immunocompromised patients.[17] However, it is hard to balance the risk and benefit of re-vaccination for patients during chemotherapy in an outbreak setting, and no existing evidence can be used to guide this practice. Thus, postexposure immunoglobulins prophylaxis is usually implemented for this special group.

In this study, we noticed that all patients except the first patient had hospital visit histories within 7–21 days before measles onset. Moreover, 17 patients from hospital B and three patients from hospital A were likely to be exposed to each other, highly suggestive of an outbreak of measles due to nosocomial infection. Several studies from China showed hospital visit was the major risk factor for measles transmission and outbreak in children and adults.[19-21] Currently, nosocomial transmission is an important mode

Table 2: Clinical and laboratory findings of measles in pediatric hematology and oncology patients in Shanghai, 2015

Case number*	Tmax (°C)	Fever duration (days)	Cough	Hoarseness	Conjunctivitis	Rash (any)	Koplik's spot	Leucopenia/ neutropenia†
1	40.4	8	Yes	Yes	Yes	Yes	Yes	No/no
2	39.9	12	Yes	No	Yes	Yes	No	Yes/yes
3	39.7	5	Yes	No	Yes	Yes	Yes	Yes/no
4	39.9	18	Yes	No	Yes	Yes	Yes	Yes/no
5	39.8	13	Yes	No	No	Yes	No	No/no
6	39.4	8	Yes	No	Yes	Yes	Yes	Yes/yes
7	40.0	9	Yes	Yes	Yes	Yes	No	Yes/no
8	39.5	2	No	No	No	No	No	Yes/yes
9	38.4	3	Yes	No	No	No	No	Yes/no
10	39.0	5	Yes	No	No	Yes	Yes	Yes/yes
11	38.0	6	Yes	Yes	Yes	Yes	No	Yes/no
12	39.3	10	Yes	No	No	Yes	Yes	No/no
13	39.3	5	Yes	Yes	Yes	Yes	Yes	Yes/yes
14	38.6	5	Yes	No	No	Yes	No	Yes/yes
15	39.5	30	Yes	No	No	No	No	No/no
16	40.0	10	Yes	No	Yes	Yes	Yes	No/no
17	39.3	3	Yes	No	Yes	Yes	Yes	No/no
18	40.4	5	Yes	No	No	No	No	No/no
19	39.7	20	Yes	Yes	Yes	No	Yes	No/no
20	41.0	16	No	No	No	Yes	No	Yes/no
21	40.0	14	Yes	No	Yes	Yes	Yes	Yes/no
22	40.6	7	Yes	No	Yes	Yes	Yes	No/no
23	39.8	16	Yes	No	Yes	Yes	Yes	Yes/no

Case number*	CRP/PCT‡ ([mg/L]/[ng/ml])	Diagnostic test (IgM/RNA)	Complication	Mechanical ventilation	IVIG (g/kg)	Antibiotic treatment	Outcome
1	67/0.48	+/+	Pneumonia	No	0.50	Yes	Survived
2	>160/1.23	+/+	Pneumonia	Yes	1.00	Yes	Died
3	10/0.24	+/+	No	No	0.25	No	Survived
4	>160/0.30	+/+	ARDS	Yes	1.00	Yes	Died
5	>160/0.88	+/+	Severe pneumonia (pulmonary edema)	Yes	1.00	Yes	Died
6	51/0.25	+/+	No	No	1.00	Yes	Survived
7	<8/0.13	+/+	Pneumonia	No	1.00	No	Survived
8	65/0.60	+/+	No	No	1.00	Yes	Survived
9	18/0.12	+/+	Pneumonia	No	0.50	No	Survived
10	14/0.16	+/+	No	No	1.00	Yes	Survived
11	20/0.12	+/+	Pneumonia	No	0.50	Yes	Survived
12	25/0.07	+/+	Pneumonia	No	0.40	Yes	Survived
13	<8/0.10	+/+	No	No	1.00	Yes	Survived
14	18/0.41	+/−	Pneumonia (pleural effusion)	No	0.70	No	Survived
15	104/1.43	+/+	No	No	1.00	Yes	Survived
16	35/0.37	+/+	No	No	0	Yes	Survived
17	<8/0.06	+/+	No	No	1.00	No	Survived
18	45/0.09	+/+	No	No	0	Yes	Survived
19	>160/0.51	+/+	ARDS	Yes	3.50	Yes	Died
20	>160/NA	+/+	Liver function failure	No§	2.00	Yes	Died
21	20/0.19	+/+	Severe pneumonia	Yes	1.00	Yes	Survived
22	<8/0.27	+/+	No	No	1.00	No	Survived
23	54/0.53	−/+‖	Pneumonia	No	2.00	Yes	Survived

*Sorted by the date of measles onset; †It means if they had leucopenia or neutropenia during the course of measles; ‡The value in the table showed the maximum value in the course of illness; §Parents refused to receive intubation and mechanical ventilation for baby; ‖Measles IgM antibody was negative in two paired sera samples, and measles was confirmed based on clinical features and the positive virus RNA in throat swab. Tmax: The maximum body temperature during the illness; IVIG: Intravenous immunoglobulinsW; ARDS: Acute respiratory distress syndrome; CRP: C-reactive protein; PCT: Procalcitonin; NA: Not available.

of measles exposure in developed countries where measles is largely under control.[22] Furthermore, patients exposed to measles in hospital setting may be at increased risk for a severe outcome given their underlying medical condition.[23,24] Serious complications and high mortality occurred in our serial patients. These findings highlight the importance of strict implementation of hospital infection control practices. The early recognition of suspected measles cases is crucial for timely infection control procedures. However, we observed that the manifestations of measles in malignancy children are quite atypical. Unlike the typical measles, 43.5% of breakthrough measles in vaccinated immunocompromised children did not present Koplik's spot, 21.7% did not present rash, and 8.7% did not present cough. The difficulty in clinical recognition of modified measles in vaccinated immunocompromised patients will inevitably delay the timely infection control procedures. In addition, we found measles-specific IgM antibody negative in two paired sera samples of one vaccinated patient who was positive for measles virus RNA in throat swab. Previous literature documented that the measles-specific IgM response may be either short-lived or absent in vaccinated person.[25,26] Thus, clinicians should keep vigilant about modified measles during the outbreak in vaccinated patients and diagnostic testing for measles should include both serologic and virological testing.

The immunocompromised children are not only at high-risk of developing severe vaccine-preventable infectious diseases but may also serve as a reservoir for transmission of pathogens in susceptible population. Nevertheless, vaccination and revaccination of special immunocompromised children in our country are neglected, mostly due to the concerns about the risk for adverse events of vaccination overweighs the benefit of vaccination among physicians and parents. Future personalized strategies for measles vaccination in special immunocompromised patients should be made to address the prevention of vaccine-preventable infectious diseases in this high-risk pediatric group. Meanwhile, improved hospital infection control practice is critical to protect immunocompromised patients and avoid nosocomial transmission of measles.

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Conflicts of interest

There are no conflicts of interest.

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