DISTRIBUTION OF SERUM MEASLES-NEUTRALIZING ANTIBODIES ACCORDING TO AGE IN WOMEN OF CHILDBEARING AGE IN FRANCE IN 2005–2006
IMPACT OF ROUTINE IMMUNIZATION

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Abstract: Measles antibody titers were measured in 210 French women. Ninety-four percent had protective values (>120 mIU/mL). Geometric mean titers were significantly different ($P < 0.001$) between women born before and after 1983, when measles vaccination was recommended (731 and 1358 mIU/mL, respectively). geometric mean titers in 4 age cohorts decreased significantly ($P < 0.001$) with increasing birth year. These data may help identify the appropriate age for infant vaccination.

Key Words: measles antibody, measles immunity, women, measles vaccination

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The introduction of vaccines has led to a marked decrease in the incidence of measles in industrialized countries in the past 20 years. In France, the estimated number of measles cases has dropped from 484,000 in 1980 to 331,000 in 1985 and ~4500 in 2004.[1,2] However, with vaccination coverage around 85%, France is currently below the 95% coverage level required for measles elimination,[3] and epidemiologic conditions are still favorable for outbreaks.[1,4]

During the first months of life, newborns are passively protected from measles infection by maternal antibodies. Because this passive protection may impede the response to vaccination,[5] it is important to determine the amount of maternal antibodies, which is affected by the mother's vaccination status and the overall vaccination coverage of the population. Vaccine-induced antibody titers are lower than those occurring after natural infection, and natural boosting from wild-type infections occurs less frequently in a well-vaccinated population.

To evaluate the impact of vaccination coverage on measles antibody titers in women in France, the antibody titers in women born between 1965 and 1994 were measured. These women were at or close to childbearing age (12–40 years) at the time of the study. Titers in women born before 1983 were compared with those born after this date to evaluate the impact of routine measles vaccination for 12–15-month-old infants, which has been recommended in France in 1983.[2]

METHODS

This was a multicenter, prospective, seroepidemiologic study carried out in France between October 2005 and May 2006. Eligible subjects were women at or close to childbearing age (12–40 years) at the time of the study, ie, born between 1965 and 1994, who had been living in mainland France for more than 3 years. Subjects were consecutively recruited from patients consulting or hospitalized at pediatrics and maternity departments of 7 participating hospitals and for whom a serum or blood sample was available. The protocol was reviewed and approved by each participating institution in accordance with the French law on epidemiologic studies. All subjects (and the parents of minors [<18 years]) were required to give their verbal consent to participate in the study. Patients with an underlying immunodeficiency, an infectious disease, or having received a blood transfusion were excluded.

Serum measles-neutralizing antibodies were measured at the Virus Reference Department of the Centre for Infections of the English Health Protection Agency by the plaque reduction neutralization reference assay, according to international standard operating procedures. The protection threshold was defined as >120 mIU/mL.[6]

For analysis, subjects were classified into 2 groups: women born before and after 1983, date of the introduction of measles vaccination into the French immunization calendar. Each group was further divided into 2 cohorts according to birth date: adolescents (12–18 years of age) and young women (19–22 years) born after 1983, and women born before 1983, aged 23–30 years and 31–40 years at inclusion in the study.

The Napierian logarithms of measles antibody titers in women born before 1983 and those born after 1983 were compared with a Student's *t* test. Comparisons between the 4 birth cohorts (1965–1974, 1975–1983, 1984–1987, 1988–1994) were performed on the Napierian logarithms of measles antibody titers using analysis of variance.

RESULTS

Two hundred and ten female subjects born between 1965 and 1994 were included in the study. The average age was 24.3 years and 94% of subjects had a measles antibody titer >120 mIU/mL. The geometric mean titer (GMT) of the population under study was 1038 mIU/mL. The difference in GMTs for women born before 1983 and those born after 1983 was statistically significant ($P < 0.001$); 1358 mIU/mL (95% CI: 1060–1739) and 731 mIU/mL (95% CI: 571–935), respectively. The comparison of the 4 birth cohorts shows a significant decrease ($P < 0.001$) in GMTs of serum measles-neutralizing antibodies in the female population with increasing birth year (Table 1).

DISCUSSION

To the best of our knowledge, this is the first study of measles serology in a French female population. Most of the population studied (94%) had protective immunity against measles well over threshold levels. A significant difference ($P < 0.001$) was observed between measles-neutralizing antibody titers of women born before and after 1983, with a clear-cut decrease in GMTs after 1983, the year in which routine vaccination was recommended.

National vaccine coverage for 24-month-old infants in France increased from 19% in 1979 to 32% in 1985 and 80% in 1994, to reach a current plateau of approximately 85%.[1,2] The decrease observed in measles antibody titers with increasing birth year may reflect the increase in vaccine coverage. Lower concentrations of measles antibodies in women born after 1983 could reflect an increasing number of women with a vaccine-induced immune response and an associated decrease in subsequent boosting from circulating wild virus. A similar effect has previously been reported in the United States,[7] Europe,[8,9] and South America.[10]

Because the GMT of measles antibodies in women of childbearing age in France is decreasing, passive maternal pro-

TABLE 1. Measles Antibodies Geometric Mean Titers (GMT) and Seroprotection Rates in French Women Born During 1965–1994

Date of Birth	Before 1983 (n = 119)		After 1983 (n = 91)		Test
Measles antibody GMT (95%CI), mIU/mL	1358 (1060–1739)		731 (571–935)		$P < 0.001$
Birth Cohort	1 (1965–1974)	2 (1975–1983)	3 (1984–1987)	4 (1988–1994)	Test
n	52	67	43	48	
Measles antibody GMT (95%CI), mIU/mL	1814 (1265–2601)	1084 (774–1519)	808 (534–1224)	668 (496–899)	$P < 0.001$
Seroprotection rate (% of women with measles antibody titer >120 mIU/mL)	98.1	94.0	88.4	95.8	

tection of newborns probably lasts for a shorter time than in previous decades and may continue to decrease in the coming years. A study examining measles antibody titers in 0-15-month-old French infants is currently underway to evaluate the persistence of passive immunity.

As long as the measles virus is still circulating in the environment, there is a "window of opportunity" for infections (and the consequent risk of severe disease in infants) between the loss of maternal protection and the start of vaccine-induced immunity. It is important to vaccinate infants early enough to close this window because morbidity/mortality, particularly in terms of bacterial superinfections and subacute sclerosing encephalitis, is highest in children less than 1 year of age.[11–13]

The results of this study strongly support the changes to measles, mumps, and rubella vaccination recommendations in France made in 2005[14] that reduced the age at first dose from 12–15 months to 12 months with the second dose between 13 and 24 months. Measles vaccination was recommended at 9 months for children attending communal daycare with the second dose between 12 and 15 months.[14,15] Switzerland has also lowered the age of measles, mumps, rubella vaccination from 12–15 months to 12 months and even earlier for at-risk infants.[16]

Choosing the ideal age at which to vaccinate is a balance between providing optimum vaccine-induced protection while minimizing the risk of morbidity and mortality. It is therefore important to monitor vaccine coverage and its effects on antibody titers in women of childbearing age.

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THE CHARACTERIZATION OF CEREBROSPINAL FLUID AND SERUM CYTOKINES IN PATIENTS WITH KAWASAKI DISEASE

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Background: The central nervous system (CNS) inflammation of Kawasaki disease (KD) has not been sufficiently evaluated in spite of the complications of irritability and CSF pleocytosis.

Patients and Methods: Cerebrospinal fluid (CSF) and serum inflammatory cytokine values were simultaneously examined in 10 patients (2.6 ± 2.1 year of age) during the acute phase. They were all irritable and demonstrated mild consciousness disturbance.

Results: The CSF IL6 was elevated (>3.0 pg/mL) in 6 patients, and 4 of them showed higher CSF than serum values. The CSF sTNFR1 was elevated (>0.5 μg/mL) in 6 patients, and 1 showed higher CSF than serum values. These CSF cytokine (IL6; 81.4 ± 192.8 pg/mL, sTNFR1; 1.1 ± 0.8 μg/mL) and CSF/serum ratio (IL6; 2.8 ± 5.2, sTNFR1 0.4 ± 0.4) in patients with KD were the same as those of patients with acute encephalitis/acute encephalopathy.

Conclusions: The differences in the inflammatory cytokine value between CSF and serum suggest that the degree of systemic vasculitis is different between CSF and the circulating blood, and some patients with KD showed a higher degree of CSF inflammation.

Key Words: Kawasaki disease, IL6, soluble TNF receptor 1, cerebrospinal fluid, central nervous system

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Kawasaki disease (KD) was first described in 1967 as an acute febrile mucocutaneous lymph node syndrome during infancy and early childhood.[1] The basic etiology remains unknown. In spite of a prolonged high fever, irritability, cerebrospinal fluid (CSF) pleocytosis,[2,3] and other central nervous system (CNS) involvements[4–6] during the acute phase and long-term follow-up periods, CSF inflammatory cytokines at the acute phase have not been evaluated.

To elucidate the CNS inflammation in KD, the site differences in the inflammatory cytokine/soluble cytokine receptor values between the CSF and serum were evaluated during the acute phase.

PATIENTS AND METHODS

Ten patients with KD based on the diagnostic criteria included 7 boys and 3 girls, 4 months to 6 years 8 months old, mean 2.6 ± 2.1 years of age, were evaluated at Oita University Hospital from January 2006 to December 2006. No patient had convulsions, but all were irritable with mild disturbance of consciousness. The clinical characterizations and profiles of the patients and the laboratory data are noted in Table 1 (shown in the online version only).

As age-matched disease controls, we enrolled 12 patients with acute encephalitis/acute encephalopathy. They were 2.5 ± 3.1 years of age and ill for 0.9 ± 0.5 days. Seven patients had febrile convulsion complex form (FC), a convulsion triggered by a high fever and persisting for more than 15 minutes and/or repeated convulsions with no evidence of meningitis, encephalitis, and encephalopathy, 2.1 ± 1.4 years of age, day 0.5 ± 0.2 of illness, and 9 afebrile patients with minor neurologic problem and normal CSF cells/proteins such as psychomotor retardation and failure to thrive (MNP), 2.9 ± 2.3 years of age, were compared with the patients with KD.

CSF and Serum. The CSF and blood of the KD patients, as described above, were simultaneously examined after obtaining the parents' informed consent to determine the CSF and serum cytokine profiles on day 5.8 ± 2.6 of illness, based on the diagnosis of meningitis/encephalitis and other CNS disorders. Samples were obtained before the administration of high-doses of γ-globulin. The sera were separated by centrifugation. The sera and CSF were stored at −20°C before the cytokine assay.

Cytokine Assay. IL6 (interleukin 6), sTNFR1 (soluble tumor necrosis factor receptor 1), and sIL2R (soluble interleukin 2 receptor) were examined using a human ELISA kit (Amersham Life Science, UK). The detection limits were 0.5 pg/mL, 0.05 μg/mL, and 54.5 IU/mL, respectively. A statistical examination was performed using the Mann–Whitney *U* test.

RESULTS

CSF Cells and Protein Values. As described in Table 1, 7 of 10 patients with KD showed CSF pleocytosis (more than 15/3 μL). Elevated CSF protein levels (more than 32 mg/dL) were noted in 4 patients with KD.

IL6. As described in Table 2 (shown in online version only) and Figure 1, mean CSF IL6 was 81.4 ± 192.8 pg/mL and CSF/serum ratio was 2.8 ± 5.2 in patients with KD. Six patients showed elevated CSF and in 4 of them CSF IL6 was greater than serum IL6; CSF/serum ratio was 2.95, 4.33, 17.14, and 2.60 for the 4 patients.

The control patients with encephalitis/encephalopathy (CSF, 98.3 ± 155.8 pg/mL; CSF/serum, 79.6±155.8) had elevated CSF IL6 and CSF/serum ratio. The patients with non-CNS inflammatory disease such as FC (CSF, 1.7 ± 4.7 pg/mL; CSF/serum, 0.3 ± 0.5) and MNP (CSF, 0.6 ± 0.2 pg/mL; CSF/serum, 1.1 ± 0.3) did not.

sTNFR1. As shown in Table 2, CSF values were 1.1 ± 0.8 μg/mL and CSF/serum ratio was 0.4 ± 0.4 in patients with KD. Six patients had elevated CSF values and one of them had higher CSF than serum values; CSF/serum ratio was 1.3.

The control patients with encephalitis/encephalopathy (CSF, 1.4 ± 0.8 μg/mL; CSF/serum, 0.9 ± 0.7) also had elevated CSF values, the patients with FC (CSF, 0.6 ± 0.8 μg/mL; CSF/serum, 0.6 ± 0.1) and MNP (CSF, 0.3 ± 0.1 μg/mL; CSF/serum, 0.2 ± 0.1) did not.

sIL2R. As described in Table 2, the serum sIL2R was elevated in all patients with KD, encephalitis/encephalopathy, and FC, but not detected in CSF, as was the case for control patients.

DISCUSSION

In this study, 7 of 10 patients with the acute of KD showed CSF pleocytosis, and 4 had an elevated CSF/serum ratio of IL6 and 1 showed of sTNFR1. A previous report showed that 40% of patients with KD had CSF pleocytosis[2]; it was speculated to be the result of the symptoms of systemic vasculitis or the result of vascular leakage through the blood-brain barrier.[2,3] If CSF pleocytosis in these patients was from inflammation of systemic vasculitis, then the CSF inflammatory cytokines might be similar to those seen in the serum or lower. These patients showing an elevated CSF/serum ratio did not have different neurologic symptoms than those of other patients with KD.

The elevation of the serum IL6, sTNFR1, and sIL2R play a major role in the pathogenesis of systemic vasculitis, including KD.[7,8] IL6 is not only produced by T cells and monocytes, but also by oligodendrocytes, astrocytes, and other glia cells in CNS.[9] The differences in the IL6 values between CSF and serum may suggest that the degree of inflammation is different between CSF and the circulating blood. The data in the control patients suggest that the CSF/serum ratio of IL6 increased only in the patients in whom CNS was predominantly involved. Therefore, their CSF IL6 might not be the result of vascular leakage of peripheral T cells through blood-brain barrier, but instead be the result of independent CNS inflammation caused by CNS T cells, monocytes, astrocytes, and other glia cells.

Although previous reports showed CNS involvement in KD, such as facial palsy, seizures, and cerebral artery stenosis, Moya-

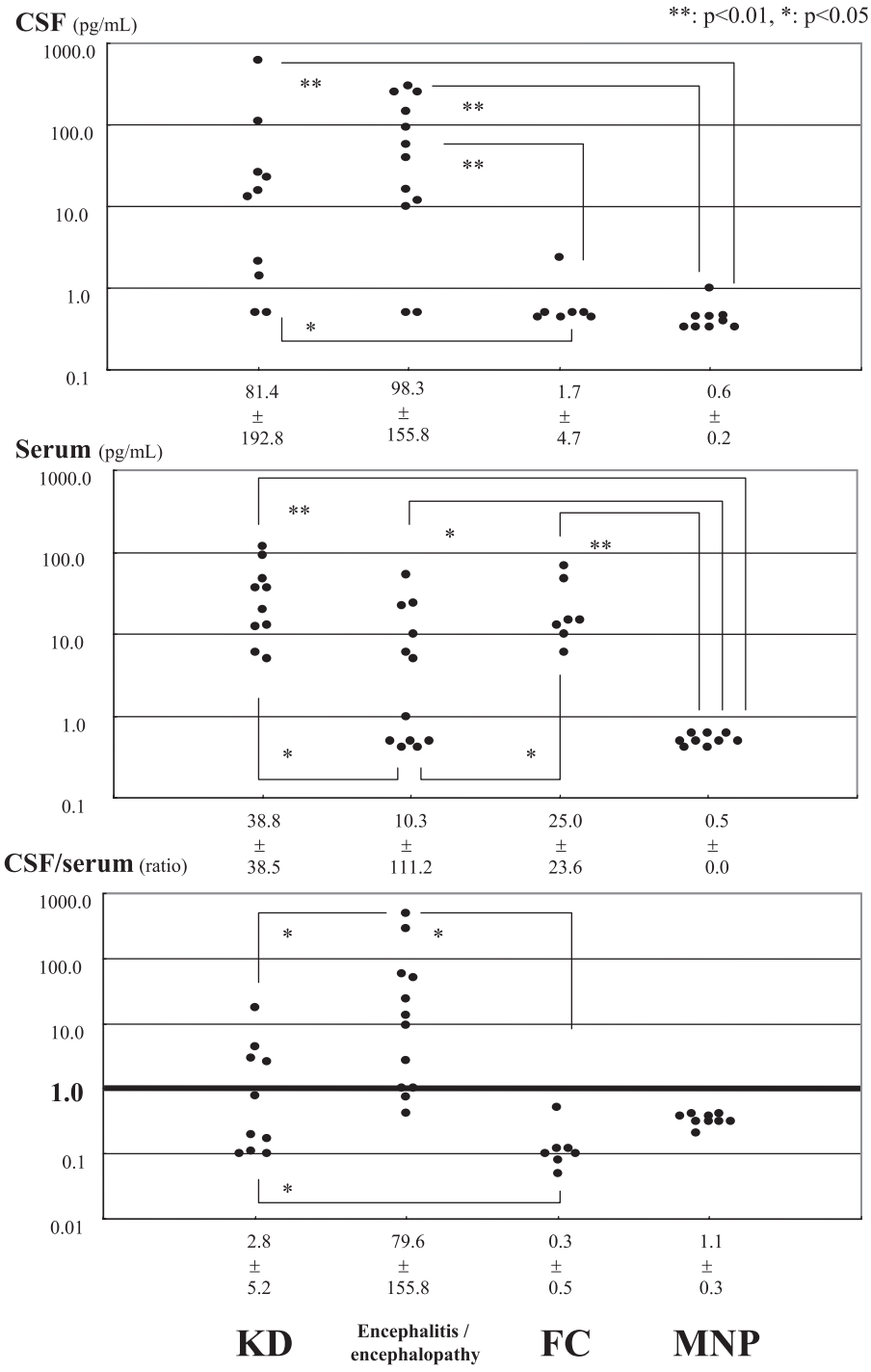

FIGURE 1. The IL6 profiles of CSF, serum, and CSF/serum ratio (KD, Kawasaki disease, acute encephalitis/acute encephalopathy; FC, febrile convulsion complex form; MNP, minor neurologic problem with normal CSF findings).

moya syndrome occurs in only 0.4%–3.7%.[4–6] King et al[10] reported using a cohort analytic study in post-KD patients with deficits in internalizing and attentional behavior; the risk of a clinically significant behavioral score was 3.3 times greater.

Because this study investigated only 10 patients with KD, and the follow-up periods of these patients were short, the relationships between the elevated CSF inflammatory cytokines during the acute phase and their long-term CNS outcomes remain unclear.

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CORONAVIRUS-ASSOCIATED PNEUMONIA IN PREVIOUSLY HEALTHY CHILDREN

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Abstract: The extent to which coronaviruses are associated with lower respiratory tract disease in previously healthy children without underlying medical conditions is unknown. We investigated instances of radiographically confirmed lower respiratory tract disease among symptomatic children with coronavirus infection. Here, we document the clinical courses of 2 previously healthy children with coronavirus-associated pneumonia.

Key Words: coronavirus, lower respiratory tract disease, viral pneumonia, children
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The contribution of non-SARS coronaviruses to acute lower respiratory tract disease in previously healthy children is unknown. Most pediatric coronavirus infections result in relatively mild upper respiratory tract illness, whereas these viruses have been associated with severe lower respiratory tract diseases (eg, bronchiolitis and pneumonia) in children with high-risk medical conditions, such as those with asthma, immunosuppression, or significant prematurity.[1–3] Improved methods of viral discovery have facilitated the recent identification of 2 novel group 1 and 2 human coronavirus subtypes—NL63 and HKU1—and a more accurate clinical epidemiology of coronavirus infection is beginning to emerge.[4,5] However, it remains unclear to what extent coronaviruses are associated with lower respiratory tract disease in previously healthy children without underlying illnesses. Few data have been presented on the subject, and the full clinical course and outcome of a previously healthy child with coronavirus-associated pneumonia has not yet been detailed in the literature.

We investigated instances of radiographically confirmed lower respiratory tract disease in previously healthy children with coronavirus infection. From a group of 56 coronavirus-positive children of 828 children who presented with respiratory symptoms to a tertiary-care hospital during a 1-year period[6] we retrospectively identified those who (a) were previously healthy without any evidence of underlying pulmonary, cardiac, renal/hepatic, or central nervous system disease, immunosuppression, or history of prematurity, (b) had only coronavirus present in their respiratory specimen as detected by reverse transcription polymerase chain reaction (RT-PCR) assays[6,7] of 14 respiratory viruses, including respiratory syncytial virus (RSV), adenovirus, influenza viruses A and B, parainfluenza virus (PIV) types 1–4, human metapneumovirus (hMPV), rhinovirus, and all 4 non-SARS coronavirus subtypes, and (c) had a chest radiograph obtained within 24 hours preceding or after their positive respiratory sample.

Twenty-one children had an isolated coronavirus infection and chest radiograph. Most (81%) had underlying medical conditions. Four children met all 3 of the above criteria and 2 (50%) had radiographic evidence of pneumonia as confirmed by a pediatric infectious disease specialist and 2 independent radiologists; 1 read the films in real time and had limited knowledge of the clinical findings, and 1 read the films retrospectively and had no knowledge of the clinical findings. Here we describe the clinical courses of these 2 previously healthy children.

CASE STUDY 1

A 14-month-old previously healthy girl was admitted to the hospital for respiratory distress and evaluation of an abnormal chest radiograph after 5 days of fever, runny nose, and nasal congestion. Before admission, she was evaluated 3 times: twice by her primary physician who diagnosed her with a viral URI and conjunctivitis, and once in the emergency room (ER) at a local community hospital where she had a chest radiograph, which was abnormal. In this interval she received only antimicrobial eye-drops. On day 6 of illness she developed a cough, posttussive emesis, and poor oral intake, and was taken to the ER at Children's Hospital and Regional Medical Center.

At admission, she had 96% oxygen saturation on room air and decreased breath sounds on the right side. A chest radiograph demonstrated a large, relatively lucent, rounded shadow with sharp borders in the right posterior mediastinum (Fig. 1A, Chest Radiograph—Right Mediastinal Opacity; available online). Laboratory findings were significant for a leukocytosis (white blood cell count of 17,800/mm^3 with 27% bands) and an elevated erythrocyte sedimentation rate (55 seconds). She was then admitted and treated empirically with intravenous cefuroxime. A follow-up computed tomography scan of her chest showed consolidation of the posterior and superior segments of the right lower lobe, with surrounding ground glass opacities (Fig. 1B, CT Scan—Right Lower Lobe Consolidation; available online).

Her nasal wash specimen was negative on florescent antibody assays for multiple respiratory viruses, including RSV, adenovirus, influenza viruses A and B, and PIV types 1–3, and later the specimen was found to be negative on RT-PCR[6,7] for the above viruses and additionally for rhinovirus, PIV type 4, hMPV, and coronavirus subtypes 229E, NL63, and HKU1. Coronavirus subtype OC43 was the sole viral respiratory pathogen detectable by RT-PCR of her original nasal wash specimen. Bacterial cultures of her blood remained negative.

The patient's clinical course was uncomplicated. She had a mild fever of 38.2°C on the first day of admission, but improved throughout the rest of her hospitalization, remaining afebrile without an oxygen requirement. She was discharged on hospital day 3 to complete a 10-day course of oral cefuroxime.

CASE STUDY 2

A 3-month-old previously healthy boy was admitted to the hospital with fever, respiratory distress, and radiographic evidence of pneumonia after 7 days of acute coryza and progressively wors-

ening respiratory symptoms. Before admission, he presented multiple times to the ER and was given amoxicillin when a chest radiograph revealed an early right lower-lobe pneumonia. Despite this therapy, he had increased work of breathing, culminating in an episode of cyanosis that lasted several minutes and prompted admission to Children's Hospital and Regional Medical Center.

On initial examination, the patient had a temperature of 38.0°C, a significantly elevated white blood cell count of 27,800/mm^3, and an oxygen saturation of 89% for several minutes, which responded to supplemental oxygen. Lung examination was notable for scattered rhonchi and mild subcostal retractions, and a chest radiograph showed diffuse interstitial infiltrates and a right-sided pleural effusion (Fig. 2 Chest radiograph of coronavirus-associated pneumonia with right pleural effusion in Case Study 2; available online). Despite intravenous fluids and antibiotics (cefuroxime), he continued to develop increased work of breathing with mild desaturations (94%–97%) and inadequate perfusion. He then became febrile (39.1°C) and was transferred to the infant intensive care unit for closer monitoring. There, he had intermittent fevers and received nebulized albuterol therapy and oxygen as required, but his pulmonary status remained relatively stable overall. A subsequent chest radiograph showed a reduced pleural effusion without significant infiltrates. He was transferred back to the general pediatric ward on the third day of admission and there he remained afebrile, was weaned off supplemental oxygen, and was discharged home on oral cefuroxime.

Immunofluorescence and RT-PCR assays of this patient's nasal wash specimen were negative for all respiratory viruses described previously, and multiple blood cultures remained negative through 5 days. The newly described coronavirus subtype HKU1 was the only viral respiratory pathogen detectable by RT-PCR analysis of his nasal wash specimen.

DISCUSSION

In these 2 cases, retrospective analysis by RT-PCR confirmed an association between coronavirus infection and radiographically confirmed pneumonia in children without underlying illnesses, immunosuppression, or a history of prematurity. Both children were the result of normal term pregnancies, and both were previously healthy without underlying medical conditions. Coronavirus subtypes OC43 and HKU1 were the only viral pathogens detected by RT-PCR in their respiratory specimens; microbiologic cultures of blood from both patients remained persistently negative. Although negative results of bacteriologic cultures cannot exclude a bacterial origin in these cases, especially given the fevers and hematologic findings noted during the acute phase of their illnesses, the detection of coronavirus as the sole viral respiratory pathogen in nasal wash specimens from these children is important. We speculate that coronavirus subtypes may play a pathogenic role in lower respiratory tract disease—either alone or with a bacterial copathogen—even among previously healthy children.

Recently in South Africa, a large randomized controlled trial of a 9-valent pneumococcal conjugate vaccine demonstrated a significant reduction in bacterial pneumonias[8] and in pneumonias attributed to respiratory viruses.[9,10] These studies argue that infection with hMPV[10] and other common respiratory viruses such as RSV, influenza A, and PIV types 1–3[9] may predispose children to bacterial pneumonias. No such data exist for coronavirus infection.

Shortly after the discovery of coronavirus in the late 1960s, this novel pathogen was found to account for a portion of previously unexplained respiratory disease in children. Using serologic methods, McIntosh et al[11] demonstrated rising antibody titers to group 1 coronavirus subtype 229E and group 2 subtype OC43 in 7.9% of 380 serum samples collected from infants (<18 months of age) hospitalized with pneumonia or bronchiolitis between 1967 and 1970. The prevalence of underlying illnesses among infected children was not reported in this study. Recently, more sophisticated viral detection methods have enabled the identification of 2 novel human coronavirus subtypes—NL63 (group 1) and HKU1 (group 2).[4,5] Several studies have now more accurately characterized the spectrum of acute clinical illnesses associated with coronavirus infection,[4,5,12–14] but clinical information on coronavirus-associated lower respiratory tract disease among previously healthy children remains limited.

In a study from Hong Kong by Chiu et al[13], 26 of 587 hospitalized children had coronavirus NL63, OC43, or 229E detected from respiratory specimens by RT-PCR. Seven patients without underlying conditions had NL63 as the sole pathogen detected, and only 3 showed evidence of lower respiratory tract disease. All 3 had cough and stridor, did not have chest radiographs documented, and were diagnosed with croup. Of the 4 previously healthy children with only OC43 detected, 1 child had a radiographically confirmed lower-lobe infiltrate[13]. Similarly, Esper et al[14] examined specimens from 851 children to identify 9 with HKU1 as the sole respiratory pathogen as determined by direct immunofluorescence for influenza, PIV types 1–3, RSV, and adenovirus, and by RT-PCR for hMPV and coronavirus subtypes HKU1 and NH (an NL63-like coronavirus subtype). They documented 2 previously healthy HKU1-infected children with radiographic evidence of pneumonia. Although these 2 children did not have further RT-PCR testing for respiratory viruses, which may be more sensitive than direct immunofluorescence assays,[7,15] these data are consistent with our findings that lower respiratory tract disease may be associated with coronavirus infection in previously healthy children without underlying conditions.

Although historically considered a benign pathogen responsible for common colds, coronavirus is associated with more severe respiratory illnesses in the presence of predisposing risk factors. We have demonstrated here that coronavirus may also play a pathogenic role—either alone or possibly with a bacterial copathogen—in lower respiratory tract disease among children without underlying cardiopulmonary disease, immunosuppression, or a history of prematurity. The cases described in this report provide a clinical description of radiographically confirmed coronavirus-associated pneumonia in previously healthy children. Additionally, study of case 2 illustrates that coronavirus-associated pneumonias can have significant clinical consequences, resulting in infant intensive care unit admission even among children without chronic underlying health issues. We note that both subjects in this report received long-term empiric intravenous and oral antibiotics. As the contribution of coronavirus and other newly identified respiratory viruses to the overall burden of disease in young children is elucidated, a rapid and sensitive diagnostic test for detection of these viruses and for potential bacterial copathogens may ultimately provide an important means of decreasing use of antibiotics in children with viral pneumonia.

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CUTANEOUS *MYCOBACTERIUM AVIUM* COMPLEX INFECTION AS A MANIFESTATION OF THE IMMUNE RECONSTITUTION SYNDROME IN A HUMAN IMMUNODEFICIENCY VIRUS-INFECTED CHILD

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Abstract: We report a 13-year-old boy with human immunodeficiency virus infection who developed cutaneous *Mycobacterium avium* complex infection 2 months after commencing highly active antiretroviral therapy. The case illustrates that cutaneous *Mycobacterium avium* complex may present as a manifestation of the immune reconstitution syndrome in human immunodeficiency virus-infected children.

Key Words: cutaneous *Mycobacterium avium* complex, HIV, immune reconstitution

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Mycobacterium avium complex (MAC) comprises 2 closely related organisms, *M. avium* and *M. intracellulare*. MAC is a ubiquitous organism that may be acquired by inhalation or ingestion after contact with a diverse range of environmental sites, including water, soil, and animals.[1] The 3 major disease syndromes produced by MAC in humans are pulmonary disease, disseminated disease, and cervical adenitis. Rarely MAC can cause disease in other sites, including cutaneous involvement. The incidence of disseminated MAC in human immunodeficiency virus (HIV)-infected children in the era of highly active antiretroviral therapy (HAART) has fallen as compared with the pre-HAART era.[2] Other clinical manifestations of MAC in children receiving HAART have not been described.

Although cutaneous MAC has been reported in association with the immune reconstitution syndrome in HIV-infected adults, the same manifestation has not been reported in children.[3] In this manuscript, we describe a 13-year-old boy who developed cutaneous MAC 2 months after commencing HAART.

CASE REPORT

A 13-year-old African American male with recently diagnosed perinatally acquired HIV infection presented to the Emergency Department complaining of an ulcer on his right calf and intermittent fevers for 1 week. There was no history of trauma to the area, hot tub use, recent travel, or sick contacts. He had no known exposure to tuberculosis. A week before, he had been treated with oral clindamycin for presumed cellulitis with no significant change in the right calf wound despite good adherence to the regimen. He had no respiratory symptoms.

The patient was diagnosed with perinatal HIV infection after presenting with fever, weight loss, oral thrush, and inguinal lymphadenopathy. He had received HAART and prophylaxis with azithromycin and trimethoprim-sulfamethoxazole for 2 months. His HAART regimen initially consisted of zidovudine, lamivudine, and efavirenz. Before starting HAART, $CD4^+$ cell count was less than 15 cells/mm^3, $CD4^+$ percent was 1% and plasma HIV ribonucleic acid (RNA) level was greater than 100,000 copies/mL (Bayer Versant HIV-1 RNA 3.0 Assay; Bayer Corp., Tarrytown, NY). Within a month of commencing therapy, the plasma HIV RNA concentration was undetectable but the $CD4^+$ count remained low at around 15 cells/mm^3. Four weeks before admission, a protease inhibitor, lopinavir-ritonavir, was added to the existing regimen with the aim of increasing the speed of $CD4^+$ count recovery. The most recent $CD4^+$ cell count was 57 cells/mm^3 with a $CD4^+$ percent of 8 and an undetectable plasma HIV RNA concentration.

On physical inspection, the patient was a thin (weight below the fifth percentile for age), short (height below the fifth percentile for age), developmentally age-appropriate young man who was afebrile with normal vital signs. Examination revealed no oral lesions, clubbing, cardiopulmonary abnormalities, abdominal tenderness, hepatosplenomegaly, peripheral edema, or rashes. A 2×2 cm right femoral node was warm, indurated, and tender. The posterior aspect of his calf was punctuated by a tender, edematous ulcer measuring 2×2.5 cm with copious purulent drainage and an erythematous, warm rim. Laboratory tests were notable for a leukopenia (2900 white blood cells/mm^3) with a normal differential count (63% neutrophils, 27% lymphocytes, 8% monocytes, 2% eosinophils), an elevated erythrocyte sedimentation rate (97 mm/h), and a low alkaline phosphatase value (148 U/L, normal being 200–495 U/L). Gram staining of the ulcer revealed moderate white blood cells and no bacteria. Ziehl-Neelsen staining of the ulcer drainage demonstrated numerous acid-fast organisms. DNA PCR testing was not performed on the exudate because of the test's poor specificity and the potential cost of false-positive results. Findings of a cytologic examination were unremarkable. A tuberculin skin test revealed 5

mm of induration approximately 48 hours after placement. Four blood cultures for acid-fast bacilli were sterile. Three induced sputa were negative for acid-fast organisms by microscopy. An ultrasound of the right thigh lesion demonstrated an enlarged lymph node with no fluid collection. Radiographs of the right lower extremity and chest were unremarkable apart from soft-tissue swelling in the area of the ulcer.

In the setting of severe HIV-related immunodeficiency, with partial immune reconstitution 2 months after commencing HAART, acid-fast organisms found in the ulcer, a positive tuberculin skin test, and negative chest radiography and sputa for acid-fast bacilli, a presumptive diagnosis of cutaneous nontuberculous mycobacterial infection was made. Clarithromycin, ciprofloxacin, and ethambutol were added to his HAART regimen. Twelve days later, the patient was afebrile with no further drainage from the right calf ulcer and no change in the right thigh nodule. After hospital discharge, wound cultures yielded MAC susceptible to the empiric antibiotic regimen. Three of 3 induced sputa, although negative on initial staining, isolated MAC in 12–20 days with identification confirmed by DNA probe testing (ARUP laboratories, Salt Lake City, UT) and susceptibilities matching those of the wound specimen. Five months after starting HAART, and 3 months after starting therapy for MAC infection, his $CD4^+$ count is now >100 cells/mm^3, his plasma HIV RNA level remains undetectable, the ulcerative lesion has healed, and he remains asymptomatic from a pulmonary standpoint.

DISCUSSION

Cutaneous disease caused by MAC is extremely uncommon and occurs in 3 circumstances. First and most frequently, traumatic skin inoculation results in subcutaneous nodules or skin ulcers. Second, MAC cervical lymphadenitis may erode through to the skin. Third, skin involvement arises as a local manifestation of disseminated MAC, such as in acquired immunodeficiency syndrome patients with the immune reconstitution syndrome or after steroid therapy. Of the 6 pediatric cases of cutaneous MAC in the English literature, 4 HIV-uninfected cases belong to the first and third groups.[4–7] The 2 HIV-infected cases are a 6-year-old female with regional lymphadenitis and a 7-year-old boy with multiple subcutaneous nodules. They are described in a series of 9 HIV-infected children presenting with the immune reconstitution syndrome caused by nontuberculous mycobacteria.[8]

In an HIV-infected individual who has received several weeks of HAART, the cell-mediated immune response is restored, which may result in an inflammatory reaction to MAC antigens and lead to local symptoms. This manifestation of the immune reconstitution syndrome classically presents with painful lymphadenopathy 1–12 weeks after initiating HAART.[9] Cutaneous MAC in the setting of the immune reconstitution syndrome presents differently from other patients with disseminated MAC. These patients, as demonstrated in our case, have sterile blood cultures and less-prominent constitutional symptoms (fever is usually present but abdominal pain, diarrhea, weight loss, and night sweats are not).

The diagnosis of cutaneous MAC is suggested by the finding of acid-fast bacilli or granulomas in tissue but confirmation requires recovery of MAC by culture from the affected site. Skin testing with *M. tuberculosis* antigen alone, however, has limited sensitivity.[10] In our patient, 5 mm of induration after 48 hours is considered significant given his profound immune suppression. Pulmonary MAC is a more difficult diagnosis with a clinical case definition requiring a symptomatic patient with radiographic abnormalities and identification of the organism from pathologic, sputum, or bronchial wash sampling.[11] Our patient does not meet the criteria required to make a diagnosis of pulmonary MAC and the positive sputum cultures most likely represent colonization of his respiratory tract.

Successful treatment of MAC requires at least 2 and often 3 agents. Macrolides and azalides exhibit excellent in vitro activity against MAC.[12] Monotherapy is not recommended, as rates of acquired macrolide resistance are unacceptably high, approaching 46% in 1 trial, with subsequent recurrence of clinical symptoms.[13] Hence, combination therapy with agents such as rifabutin, rifampin, ethambutol, fluoroquinolones, streptomycin, or an aminoglycoside is essential in treating MAC both to maximize the effectiveness of macrolides and to minimize the development of macrolide resistance. In patients receiving HAART, drug-drug interactions need to be carefully considered in one's choice of regimen to cure disease caused by MAC while maintaining optimal plasma HIV RNA suppression. The duration of therapy in HIV-infected patients depends on the patient's immune status. Experts suggest a 1 year course in people who have had a $CD4^+$ count ≥ 100 cells/mm^3 for at least 6 months and lifelong therapy for those with a $CD4^+$ count <100 cells/mm^3.[14] MAC prophylaxis should be started in patients with $CD4^+$ counts <50 cells/mm^3 because the risk of disseminated MAC disease in the absence of prophylaxis is as high as 20% per year.[15,16] With appropriate prophylaxis, the risk of MAC infection drops to less than 10% per year.[17]

We report a case of cutaneous MAC in an HIV-infected child and discuss the pathogenesis, diagnosis, treatment, and prophylaxis of this condition. Of unique interest is the timing of the infection 2 months after the initiation of HAART. This suggests that cutaneous MAC can present as a manifestation of the immune reconstitution syndrome in HIV-infected children.

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INFECTED SUBGALEAL HEMATOMA IN A NEONATE

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Abstract: Subgaleal hematoma (SGH) is an infrequent finding in neonates, occurring mostly after vacuum extraction deliveries. SGH can cause anemia, hypovolemic shock, and death. To date, only one case of neonatal infected SGH has previously been reported. We describe a term neonate with severe polymicrobial infection complicating SGH, including anaerobic bacteria, and with unique imaging features.

Key Words: newborn infant, subgaleal hematoma, infection, anaerobic bacteria, *Staphylococcus*, *Streptococcus*

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Subgaleal hematoma (SGH) is an infrequent finding in neonates, mostly encountered after vacuum extraction (7-fold increase) or forceps delivery (2.6-fold increase).[1,2] Moderate-to-severe SGH occurs in up to 30 of 10,000 births.[2,3] SGH is caused by rupture of emissary veins, which are vascular connections between the dural sinuses and the scalp veins.[3] Large volumes of as much as 260 mL of hemorrhagic fluid can occasionally accumulate below the epicranial aponeurosis that covers the skull bones, and hence can cross interbone sutures and enlarge rapidly.[3] Of those reported cases of moderate-to-severe SGH, progressive anemia complicated by hypovolemic shock can lead to death in 11.8%–25% of cases.[2,4,5] We herein describe a neonate with SGH complicated by polymicrobial infection, and also discuss management dilemmas of this severe infection.

CLINICAL REPORT

A term female neonate was delivered using vacuum extraction, with a birth weight of 4195 g and Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Scalp monitor was not used during delivery. The parents were healthy and the pregnancy was reportedly uneventful. Physical examination in the first hour of life revealed a large-for-gestational age infant and a large SGH covering the parietal and occipital bones bilaterally. There were no scalp abrasions or lacerations. Otherwise, examination was normal. At 2 hours of life, hemoglobin value was 18 g/dL and platelet count was 76,000/mm^3. Other laboratory studies were done at 24 hours of life and included repeated platelet count that increased to 128,000/mm^3, normal coagulation studies, and normal protein C, protein S, antithrombin III activity, factor V Leiden, factor VIII, and factor XIII. No mutation was found for prothrombin; however, polymerase chain reaction showed heterozygosity for methyltetrahydrofolate reductase, a benign finding with no increased risk for hypercoagulability.

The infant was kept in the hospital for the first 5 days of life because of restlessness with excessive crying when moved or touched. On the sixth day of life, fever developed (39°C) accompanied by apathy, feeding difficulties, tachypnea, acrocyanosis, and a tense SGH. Hemoglobin decreased to 16.7 g/dL with a white blood cell count of 11,000/mm^3, neutrophils 20%, band forms 22%, lymphocytes 48%, monocytes 8%, and eosinophils 2%. Repeated PT, PTT, and INR were normal; however, the concentrations of fibrinogen (868 mg/dL; normal, 160–400 mg/dL) and D-dimers (3.31 mg/L; normal, 0–0.5 mg/L) were increased. Cultures of blood, urine, and cerebrospinal fluid (CSF) were sterile. Computed tomography (CT) of the brain on the sixth day of life revealed a large subcutaneous SGH containing air bubbles (Fig. 1). There were no bony fractures or intracerebral hemorrhages and the venous sinuses

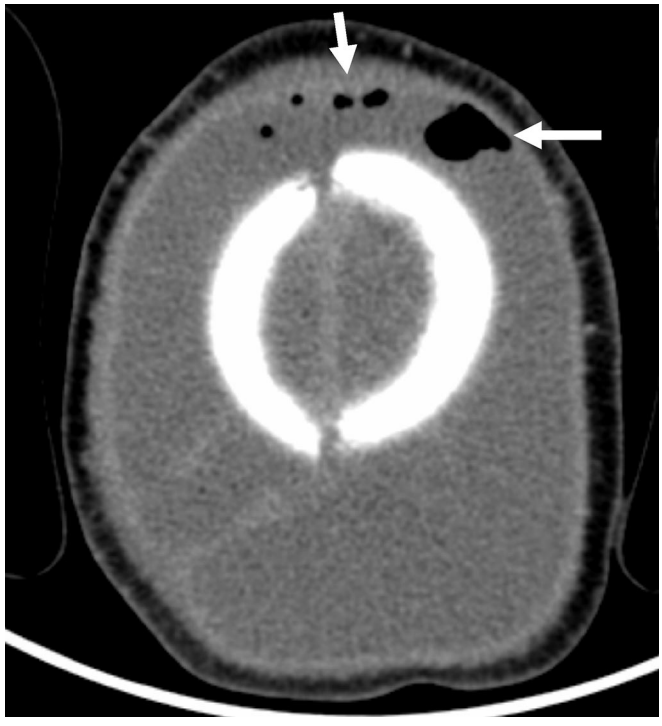

FIGURE 1. Computed tomography axial scan of the brain revealing a large subcutaneous subgaleal hematoma with air bubbles within it (arrows). The bony structures, venous sinuses, and intracranial arteries were normal (not shown).

and intracranial arteries were normal. CSF examination showed the following: fresh red blood cells 50/mm^3, neutrophils 3/mm^3, glucose 112 mg/dL, and protein 29.7 mg/dL. Vancomycin and amikacin therapy was started. Twelve hours later, a 5-mL sample of bloody material was aspirated from the SGH collection after shaving and thoroughly prepping the area with antiseptic. Piperacillin-tazobactam was added to the antibiotic regimen.

Culture from SGH aspiration specimen had polymicrobial growth, including α-hemolytic *Streptococcus* Lancefield group G (penicillin-susceptible), *Staphylococcus aureus* (methicillin-susceptible), and *Peptostreptococcus assaharolyticus* (clindamycin-susceptible). API rapid 32 ID STREP (Biomerieux) test identified the *Streptococcus* as *Streptococcus agalactiae* (87%) that was finally identified to the species level by sequencing of the 16S rRNA gene as *S. disgalacticae* subsp. *equismilis*. After receiving the bacterial susceptibility results, antimicrobial therapy was changed accordingly to dicloxacillin 200 mg/kg/d and clindamycin. Diarrhea developed while receiving antimicrobial therapy, stool culture for pathogens was negative, and a stool sample tested negative for *Clostridium difficile* toxins A and B.

Because of a further enlargement of the SGH and persistence of fever, an additional CT of the brain was performed on the 10th day of life and ruled out a continuing bleeding from the intracranial venous sinuses into the SGH space. There was no evidence for osteomyelitis of skull bones. Sequential needle drainage of SGH was then performed with aspiration of 95, 80, 85, 70, and 10 mL on the 10, 11, 14, 16, and 21st days of life, respectively. Examination of the aspirated fluid showed hemoglobin of 2.3 g/dL, white blood cells of 140,000/mm^3 with 92% neutrophils. Repeated CSF culture was sterile. Head wrapping for prevention of re-enlargement of SGH after aspiration was not successful. After the second aspiration, the hemoglobin value dropped to12.3 g/dL and a blood transfusion was administered.

Fever subsided after the second drainage (day 12), 6 days after starting antimicrobial therapy, and oral feeding was resumed. Hemoglobin value remained stable, and platelet count and fibrinogen were normalized. The size of the SGH decreased slowly accompanied by lessening of scalp tenderness and discomfort. Culture of the SGH specimen, obtained on the 21st day of life, was sterile. Antimicrobial therapy was continued for 30 days. In addition to irritability with excessive crying whenever the SGH area was touched, the infant presented with generalized hypotonia and opisthotonus. This latter finding, in the absence of meningitis, could have been due to occipital irritation by the infected SGH. These abnormal neurologic findings gradually improved along with recovery from infection. Follow-up examinations of the infant at 2 and 3 months of age, including neurologic evaluation, was normal.

DISCUSSION

We described a term neonate with polymicrobial infection complicating SGH, distinctive imaging findings, and a prolonged recovery course. A review of the English literature shows that infected cephalhematoma has previously been described in several reports.[6–8] However, infection of SGH has been previously reported only by Eggink et al[9] who described a neonate with cephalhematoma and SGH complicated by infection due to *Gardnerella vaginalis,* associated with electronic fetal monitoring. Although Chen et al[10] previously described a 34-day-old infant with subgaleal abscess, their case appears different from our case because of lack of definitive evidence of SGH in the perinatal period. Infection of cephalhematoma can be polymicrobial including anaerobic bacteria,[6–8] and can result in scalp cellulitis, osteomyelitis of skull bones, brain and scalp abscesses, meningitis, epidural and subdural empyema, sepsis, and death.[6–8] In the present case, both aerobic and anaerobic bacteria were involved in the SGH infection.

Optimizing the outcome for babies with SGH requires early diagnosis, careful monitoring, and prompt treatment.[3] Thorough physical examination of the infant at birth and awareness of the possibility of SGH after vacuum extraction were crucial for successful management in our patient. In an infant with SGH, frequent measurements of occipitofrontal circumference and monitoring of hemoglobin values every 4–8 hours are mandated in the first 24 hours.[1] Blood loss may be massive before hypovolemia becomes evident.[3]

Although not routinely performed, skull radiograph is indicated and can detect skull fractures.[4] CT or magnetic resonance imaging can reveal the amount of extra-osseous bleeding, the degree of bone displacement, and injury as well as the type and extent of associated intracranial damage.[1,4] In the present case, all aspirations from SGH were performed after brain CT was performed. The air bubbles shown by CT of the SGH collection in our case were most likely caused by anaerobic bacteria growth. These findings, together with previous reports of anaerobic infection of cephalhematomas,[6,11] imply the empiric administration of anti-anaerobic therapy, pending culture results.

Except for blood transfusion when indicated, the management approach to noninfected SGH is conservative. With infected SGH, surgical drainage would be the logical approach. However, drainage is a double-edged sword, because although the pus is drained, the "tamponade effect" is lost and rebleeding with re-enlargement of SGH occurs, leading to recurrent anemia and persistence of SGH infection. In our case, drainage led to anemia necessitating blood transfusion and could have lengthened SGH infection time. For restoring the tamponade effect that is usually lost after drainage of SGH, pressure wrapping of the head has been previously tried, but the large subaponeurotic space makes wrapping difficult. Moreover, wrapping may be disadvantageous if cerebral edema is present.[3] Newborns with SGH who survive the acute episode without brain injury at birth show no evidence of subsequent long-term neurologic deficit or developmental delay.[6] Our patient developed transient abnormal neurologic findings even though meningitis and intracranial injuries were ruled out.

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TOXIC SHOCK SYNDROME IN A NEONATE

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Abstract: We report an unusual case of toxic shock syndrome in a 4-day-old baby, with mucosal isolates of *Staphylococcus aureus* (SEC, G, and I) and group G streptococcus. Treatment involved intravenous immunoglobulin and antibiotics. This case highlights the difficulties associated with the diagnosis and treatment of this condition in neonates.

Key Words: toxic shock syndrome, *Staphylococcus aureus*, intravenous immunoglobulin, neonate

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Staphylococcal and streptococcal toxic shock syndrome (TSS) is rare in children and even rarer in neonates. This is particularly true of staphylococcal toxic shock. Although invasive neonatal group A streptococcal disease is well recognized in association with maternal carriage, neonatal streptococcal toxic shock is much less well reported.[1] We report an unusual case of TSS in a 4-day-old baby, with mucosal isolates of *Staphylococcus aureus* staphylococcal enterotoxin SEC, G, and I and group G streptococcus. We discuss the challenges associated with treatment in this age group and examine the potential benefits of intravenous immunoglobulin.

CASE REPORT

A 3-day-old male neonate was admitted with jaundice, feeding difficulties, and bile-stained vomiting. He had been born by a vacuum-assisted vaginal delivery at 42 weeks, in good condition. He was discharged home on day 1.

An initial diagnosis of malrotation was suspected. An abdominal radiograph and barium follow-through investigation were normal. Within 12 hours of presentation he rapidly deteriorated with hypotension, respiratory distress, and multiorgan failure. He was commenced on cefotaxime, amoxicillin, gentamicin, and acyclovir therapy. He required ventilation, significant multiple inotropic support, and peritoneal dialysis for renal failure.

His liver function became deranged with ALT rising to 107 IU/mL and there was evidence of disseminated intravascular coagulation. He had a focal seizure of his left arm, though subsequent MRI scan revealed no significant pathology. On day 3 of his illness he developed a generalized erythrodermic rash. TSS was suspected and flucloxacillin added (gentamicin and aciclovir had been stopped). Day 4 saw further deterioration and high dose (2 g/kg) intravenous immunoglobulin was given. Shortly afterward he began to show signs of recovery. On day 7 of his illness he developed generalized superficial skin peeling, including palms and soles. By 3 weeks he had made a full recovery.

Despite an extensive septic screen, including a normal lumbar puncture, negative CMV, adenovirus and EBV PCRs, the only positive culture was from an umbilical swab, which isolated *S. aureus* and group G streptococcus. The *S. aureus* was identified as a toxin-producing strain with SEC, G, and I identified. Multilocus sequence typing showed that it belonged to sequence type (ST) 45, and by protein A sequencing (spa) is spa type t331.

ASOT taken on day 8 of illness was significantly elevated (>800) and when repeated 6 weeks later had returned to normal.

DISCUSSION

This baby fulfils the diagnostic criteria for either staphylococcal or streptococcal TSS. Both are rare in children and even rarer in neonates, especially staphylococcal toxic shock. It is thought that TSS is mediated through a group of proteins known as superantigens.[2] These include staphylococcal enterotoxins A to E and G to I, toxic shock syndrome toxin 1 (TSST-1), and streptococcal pyrogenic exotoxins. They bind to major histocompatibility complex (MHC) class 2 molecules on antigen-presenting cells in an unconventional manner and stimulate an excessive T-cell response. This leads to a significant production of proinflammatory cytokines, hence capillary leak, hypotension, and shock.

Additionally, isolation of exotoxin-producing *S. aureus* from a mucosal site has been proposed as a further criterion.[2] This may be less useful in infants because of the high level of *S. aureus* carriage, which can be up to 50% in those less than 3 months old.[3]

Staphylococcal enterotoxin C (SEC) is now well recognized as a cause of TSS[1,2] and there is also some evidence for SEG and SEI also having a role.[4] However, not only was a toxin-producing *S. aureus* isolated, but also a group G streptococcus from the umbilical swab. This, together with the raised ASOT, suggests invasive group A, C, or G streptococcal disease. Group G streptococci can also cause toxic shock[5] and it has been postulated that dual infections with toxin-producing pathogens may produce a more severe disease.[6] This is a possible explanation for this infant's profound disease.

In Japan a new neonatal disease caused by TSST-1 has been identified.[7] As the disease did not meet the initial clinical criteria for diagnosing TSS they have called it neonatal toxic shock syndrome-like exanthemous disease. The bacteria isolated in each of those cases was MRSA. The *S. aureus* identified in our case was only one genetic mutation away from becoming MRSA. This could indicate that we are not too far away from a similar disease in the UK. Multilocus sequence typing of our isolate shows that it belongs to ST 45, and by protein A sequencing (spa) the isolate is spa type t331. ST 45 MRSAs are fairly widespread in Europe. However, none of the 17 epidemic MRSAs seen in the UK to date have been of this lineage. This suggests that our patient's isolate is not a precursor of one our epidemic strains.

Aggressive and prompt treatment with fluids, vasopressor or inotrope infusions, and β-lactamase resistant antistaphylococcal antibiotics, is crucial. Intravenous immunoglobulin has been proposed as an efficient adjunctive therapy but its effects are not well documented in staphylococcal TSS.[1] Clindamycin may be helpful as an additional treatment as it may help terminate toxin production. Its use is widely recommended in the treatment of TSS.[1] However, there have been reports of "Gasping Syndrome" in reaction to one of its excipients in neonates.[8] This makes the neonatal group a particularly challenging one to treat.

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LEGIONELLA BOZEMANII PULMONARY ABSCESS IN A PEDIATRIC ALLOGENEIC STEM CELL TRANSPLANT RECIPIENT

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Legionella spp. infections are often considered in the differential diagnosis of pneumonia in adults. This case report describes a pediatric stem cell transplant recipient presenting with cavitary pulmonary disease secondary to *Legionella bozemanii* infection. Also highlighted with this atypical clinical presentation are challenges in diagnosing legionellosis and concerns of increased vulnerability for such infections when severely immunocompromised patients are changed to nontrimethoprim-sulfamethoxazole *Pneumocystis jiroveci* pneumonia prophylaxis.

Key Words: legionella, abscess, transplant, pediatric

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Legionella species are an important cause of pneumonia in immunocompromised patients.[1,2] Although *Legionella pneumophila* is the usual pathogen, immunocompromised patients are more likely to have disease caused by non-*pneumophila* species.[3] Although most recognized for its association with pneumonia, *Legionella* spp. infection can occasionally present as pulmonary nodules some of which progress to cavitary lesions with abscess formation. This presentation has been described primarily in posttransplantation patients or those who have a clinical history of corticosteroid treatment or acquired immunodeficiency virus and is associated more commonly with *L. micdadei*.[4]

We describe a pediatric allogeneic bone marrow transplant recipient diagnosed with *L. bozemanii* pulmonary infection and discuss the clinical findings and diagnostic workup that established the diagnosis. This case is instructive of the challenges in diagnosing *Legionella* spp. infections in immunocompromised pediatric patients.

CASE DISCUSSION

A 12-year-old male patient was received in transfer with a cavitary pulmonary lesion 6 months after receipt of a related T-cell-depleted hematopoietic stem cell transplant for relapsed acute lymphoblastic leukemia. The patient was well until 3 weeks before admission when he developed weight loss, anorexia, and malaise. He subsequently developed mild rhinorrhea, occasional, nonproductive cough, and fever, prompting evaluation by his local physician. A chest radiograph and chest computed tomography (CT) scan done as part of the initial diagnostic workup revealed a right-sided cavitary pulmonary lesion. As a result, the patient was admitted and empirically treated with ceftazidime, vancomycin, and a single dose of azithromycin. During this 5-day hospital stay, he defervesced and was subsequently transferred for further management.

The patient was diagnosed with acute lymphoblastic leukemia 8 years before this admission. He sustained 2 relapses that prompted allogeneic hematopoietic stem cell transplant. Donor engraftment was confirmed 18 days after the transplant. His posttransplantation course was complicated by grade 1 graft versus host disease, developing between 100 and 139 days posttransplantation. He received cyclosporine for 4 months and daily prednisone throughout the current hospitalization. The remainder of the posttransplant course was uneventful and no acute illnesses or hospitalizations were reported. The patient was changed from trimethroprim-sulfamethoxazole (TMP-SMX) to monthly pentamidine for *Pneumocystis jiroveci* pneumonia prophylaxis 1 month before the current admission because of neutropenia requiring granulocyte colony stimulating factor.

Upon transfer, the patient was found to be afebrile, with a normal respiratory rate, and was otherwise clinically stable. His physical examination revealed decreased breath sounds in the right lower lobe without associated increased work of breathing and mild graft versus host disease manifested as dry, flaky skin. Pertinent hematologic and chemistry laboratory values were as follows: WBC 5500/mm^3 (96% neutrophils, 0% bands, 3% lymphocytes); hemoglobin 8.6 g/dL; platelets 208/mm^3; absolute neutrophil count 5100/mm^3; C-reactive protein 9.1 mg/dL (peak value during hospitalization). CT of his chest and abdomen revealed a large, 8 × 8 cm right lower-lobe cavitary lesion with associated abscess (Fig. 1), numerous bilateral pulmonary nodules, and a small, round, hypodense lesion in the spleen. Differential diagnosis at the time of admission included *Mycobacterium tuberculosis*, *Nocardia* spp., endemic mycoses, and oral anaerobic organisms. Empiric therapy was initiated with meropenem, vancomycin, azithromycin, and liposomal amphotericin B. Other diagnostic management included PPD placement (no induration was seen) and serologic tests for *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Cryptococcus neoformans*, all within normal limits and serum galactomannan test for *Aspergillus* sp, which was negative. The patient underwent a diagnostic and therapeutic aspiration of the right lower-lobe abscess, with chest tube placement, yielding approximately 20 mL of purulent material.

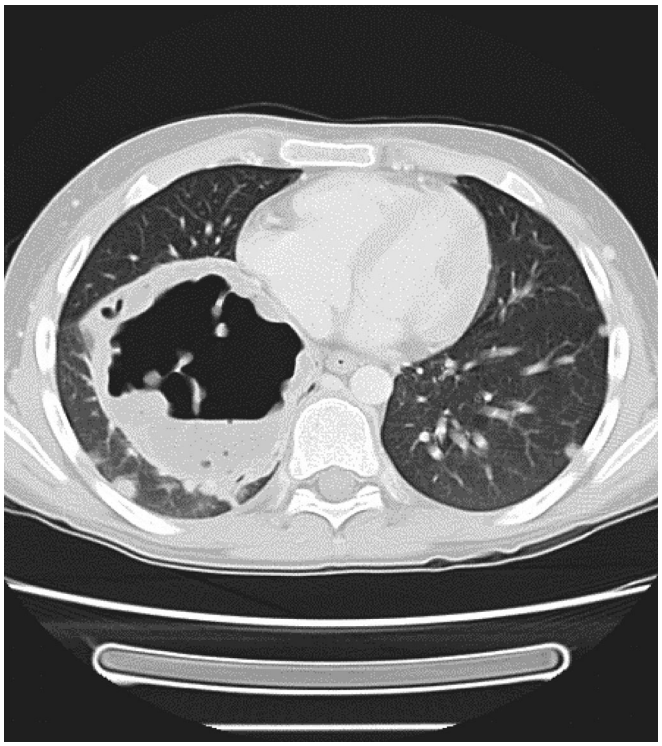

FIGURE 1. Computed tomography (CT) of chest shows a large right lower lobe cavitary lesion with associated abscess and numerous bilateral pulmonary nodules before starting antimicrobial therapy. Culture of abscess fluid grew *Legionella bozemanii.*

Initial microbiologic assessment of the aspirated chest fluid showed no organisms on Gram, calcofluor, and acid fast stainings (auramine/rhodamine and auramine O). Acid fast stain by the modified Kinyoun method showed few acid-fast organisms. At this time, the differential diagnosis included *Nocardia* sp. and *Rhodococcus equi*. Consequently, trimethoprim-sulfamethoxazole was started with continuation of meropenem; azithromycin and liposomal amphotericin B were discontinued. For the first few days after the procedure, the patient intermittently required oxygen supplementation via nasal cannula, but remained clinically well otherwise.

Growth appeared on buffered charcoal-yeast extract medium (BCYE) starting 4 days after inoculation. A presumptive laboratory diagnosis of *Legionella* spp. infection prompted resumption of azithromycin on day 7 after drainage procedure and chest tube placement. Repeat testing of the chest tube drainage 4 days after the initial specimen was collected showed identical isolates on BCYE medium. A diagnosis of *L. bozemanii* was confirmed using polymerase chain reaction (genus-level diagnosis) and DNA sequencing (species-level identification).

Follow-up CT scan 12 days after chest tube insertion revealed a decrease in size of the cavitary lesion (4.8 × 3.9 cm) and of the other lung nodules, as well as reduced communication between the lung cavity and the right lower-lobe bronchus. TMP-SMX was discontinued and the patient remained on single-agent therapy with azithromycin. Cultures for fungi, *Nocardia* spp., and mycobacteria remained negative. The patient's overall course was complicated by development of a pneumothorax that eventually resolved. Patient was discharged on azithromycin, with plans to determine cessation of therapy based upon resolution of CT findings and the patient's clinical symptoms. Five months after the diagnosis of *L. bozemanii* pulmonary disease, the patient was doing well with continued azithromycin therapy and significant improvement in his radiographic CT appearance. Given that this was an outpatient without any history of sick contacts no further epidemiologic evaluation was performed to identify the source of *Legionella* infection.

DISCUSSION

Although *Legionella* spp. have previously been reported in a few case studies as the sole agents responsible for cavitary pulmonary disease with abscess formation,[4,5] this case report, which is the first describing cavitary lung disease caused by *Legionella* spp. in a pediatric stem cell transplant recipient, serves as useful reminder of the atypical presentation of this infection in the immunocompromised host. Given the rarity of this condition, particularly in the pediatric age group, and difficulty in establishing a diagnosis unless specific cultures are ordered, this case reminds clinicians of a pathogen that is likely under diagnosed and remains a potential nosocomial pathogen.[6]

Similar to the present case, several reports have highlighted the increasing role of non-*L. pneumophila* spp. as pulmonary pathogens in immunosuppressed patients. *L. micdadei* and *L. bozemanii* are the most frequently reported species after *L. pneumophila* as causes of infection in transplant patients.[3]

The incidence of *Legionella* spp. infection in immunocompetent and immunocompromised patients is unknown, primarily because of difficulty in establishing a laboratory-confirmed diagnoses. As *Legionella* spp. require specialized media such as BCYE or targeted nucleic acid tests for detection, their presence must be suspected clinically and the appropriate tests ordered to enable rapid and definitive detection. Including *Legionella* spp. in the differential diagnosis of cavitary lung disease is therefore critical to early diagnosis and therapeutic intervention. For this patient, BCYE medium was inoculated because a *Nocardia* culture had been ordered and not because the treating clinicians had *Legionella* spp. infection in their differential diagnosis. This case also highlights the weakly acid-fast properties of this organism. Although other *Legionella* spp., particularly *L. micdadei*, have been shown to possess similar acid-fast properties, to our knowledge, this is the first report in the English literature of this characteristic in *L. bozemanii*. This case reminds clinicians to include *Legionella* spp. in the differential diagnosis of acid-fast stain positive organisms in addition to other nonmycobacterial organisms such as *R. equi* and *Brucella* sp.

It is important to remember the possibility of extrapulmonary disease in patients with pulmonary legionellosis. Although a rare occurrence, *Legionella* spp. have also been found in sites including heart, paranasal sinuses, pancreas, liver, and kidneys.[7,8] Before 2002, extrathoracic legionellosis had not been reported in the pediatric setting.[8] Our patient had a splenic nodule with CT appearance consistent with an abscess. Although culture-proven biopsy of the splenic nodule was not performed, lack of another plausible explanation combined with the knowledge that *Legionella* spp. can cause extrathoracic lesions allows reasonable inference to *Legionella* sp. as the nodule's etiologic agent.

Finally, this case highlights issues regarding the use of non-TMP-SMX *P. jiroveci* pneumonia prophylaxis. TMP-SMX is not only active against *P. jiroveci*, but is also an effective agent against *Toxoplasma gondii*, *Stenotrophomonas maltophilia*, *Listeria monocytogenes*, *Nocardia* spp., and *Legionella* spp.; its role in toxoplasmosis prophylaxis is well established. This patient was maintained on TMP-SMX for *P. jiroveci* prophylaxis until 1 month before his admission. Although the timing of infection in this patient is unclear, the replacement of TMP-SMX with pentamidine potentially in-

creased his susceptibility to *Legionella* spp. infection. The activity of TMP-SMX against other pathogens-of-importance in an immunocompromised host should be considered before switching to alternatives such as pentamidine, especially if the switch is being made for convenience.

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