MAJOR ARTICLE

Klebsiella Infection in Patients with Thalassemia

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***Klebsiella* infection has previously been reported in a few patients with transfusion-dependent thalassemia. The incidence and clinical spectrum of this infection in our cohort of patients were reviewed retrospectively. Among 160 patients observed for 12 years, there were 15 episodes of *Klebsiella* infection that occurred in 12 patients (7.5%), resulting in an incidence of 0.78 infections per 100 patient-years. The clinical spectrum included sinusitis (4 cases), intracranial infection (5 cases), septicemia (4 cases), and abscesses of the liver, lung, kidney, and parotid gland (1 case each). Three patients had recurrent infections involving different sites, 2 (16%) died of fulminant septicemia, and 3 (25%) had significant permanent neurological deficits. The antibiotic susceptibility pattern for the isolates was similar to the pattern for isolates recovered in the community. With regard to predisposing factors, iron overload and liver function derangement were found to be significant on univariate analysis ($P = .046$ and $P = .049$, respectively) but insignificant on multivariate analysis. *Klebsiella* infection was a serious and frequently encountered complication in our patients with transfusion-dependent thalassemia, resulting in high mortality and morbidity rates.**

Thalassemia is the most common single-gene disorder in the world. In Hong Kong, the rates of carriage of α-thalassemia and β-thalassemia are 5% and 3.4%, respectively [1]. The estimated number of children who had β-thalassemia major in Hong Kong in 1996 was 287 [2]. With the implementation of different means of treatment, including blood transfusion, administration of deferoxamine, and hematopoietic and cord blood stem cell transplantation [2–5], the probability of 20-year-survival for patients with thalassemia major in Hong Kong has reached 90% [6], a figure comparable to the rate in such Western countries as Italy [7].

Despite all of these treatment successes, infection has remained an important cause of death. In Hong Kong, infection was the second leading cause of death among patients not receiving hematopoietic/cord blood stem cell transplants [6], and, globally, infection has been associated with mortality rates of 12.8%–46% [8, 9]. The most well documented causative agent is *Yersinia enterocolitica.* In a cohort of patients from North America [10], 8% of patients with thalassemia had *Yersinia* infection, and the estimated incidence was 0.6 episodes per 100 patient-years; iron overload appeared to be an important risk factor for infection [10].

Klebsiella infection in patients with thalassemia has been described in a few case reports [11–13]. Nonetheless, limited data are available with regard to the incidence of infection and spectrum of clinical presentation. We performed a retrospective study of *Klebsiella* infection involving a cohort of 160 patients with transfusion-dependent thalassemia in Hong Kong during a 12-year period.

METHODS

In Hong Kong, the treatment of patients with thalassemia major is ambulatory based and is performed in

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a hospital setting; therefore, hospital records have noted most adverse events associated with this group of patients. The case records for patients with thalassemia at 3 different pediatric units in Hong Kong (Queen Mary Hospital, Queen Elizabeth Hospital, and Caritas Medical Center) were retrospectively reviewed. The cohort consisted of 160 patients, which represented ~56% of all patients in Hong Kong with thalassemia major [2].

Patient-years of observation were determined by adding the number of years of medical history available during the 12-year period. Patient age at the time of presentation, presenting features, diagnosis, treatment received, and outcomes of *Klebsiella* infection were reviewed. Possible predisposing factors, such as severity of iron overload, history of splenectomy, history of diabetes, and degree of liver derangement, were investigated for the 66 patients observed at Queen Mary Hospital.

RESULTS

Incidence of infection and patient characteristics. During the 12-year period of 1991–2002, 12 (7.5%) of 160 patients developed a total of 15 episodes of *Klebsiella* infection. This results in an incidence of 0.78 infections per 100 patient-years.

Of these 12 patients, 8 were male and 4 were female. All of the patients were receiving regular blood transfusions at the time of *Klebsiella* infection. On the basis of the serum level of ferritin (mean ± SD, 4952 ± 3311 pmol/L), all of the patients were found to have at least moderate iron overload. All but one of the patients were receiving subcutaneously administered deferoxamine at the time of diagnosis of infection. One patient (patient 11) did not receive deferoxamine after he underwent splenectomy because of poor compliance. Six patients underwent splenectomy, and 3 of the 12 patients developed diabetes mellitus as a complication of iron overload. One patient had received 2 allogeneic human leukocyte antigen–matched bone marrow transplants from a sibling donor, but the transplants failed both times. After the second transplantation, the patient developed posttransplantation marrow aplasia, which rendered him pancytopenic.

Clinical presentation, treatment, and outcome. Patient age at the time of presentation varied widely, from 9 to 22 years (median age ± SD, 15.9 ± 4.2 years). The site of infection was also highly variable: the head and neck region, the CNS, or intra-abdominal organs were sometimes involved, or the infection sometimes presented as septicemia (table 1). Two patients had multiple episodes (2 episodes in one patient and 3 episodes in the other) of *Klebsiella* infection at different sites. In addition to antibiotic treatment, surgical treatment was often necessary (for 10 of 15 episodes), either for eradication of infective material at the site of infection or for obtaining specimens for microbiological testing. Recurrent *Klebsiella* infection occurred in 2 patients in addition to the patient who had received 2 bone marrow transplants. Two patients died of fulminant *Klebsiella* septicemia, and 3 patients with CNS infection had residual neurological deficits.

Microbiological findings and antibiotic susceptibility. Of the 15 infections, 7 were caused by *Klebsiella pneumoniae,* 1 was caused by *Klebsiella pneumoniae ozaenae,* and subspecies identification was not performed for the remaining 7. All isolates were resistant to ampicillin but susceptible to aminoglycosides. Second-generation cephalosporins and trimethoprim-sulfamethoxazole (TMP-SMZ) were the second-best treatment choices, because only 1 isolate was resistant to both of them. This pattern of antibiotic susceptibility was similar to that of the strains isolated from our local community [14]. The patient who had undergone bone marrow transplantation (patient 8) had recurrent *Klebsiella* septicemia and had received prolonged courses of therapy with different antibiotics. Initially, the *Klebsiella* strains were susceptible to aminoglycosides, second-generation cephalosporins, and TMP-SMZ. However, antibiotic resistance gradually developed, and, finally, extended-spectrum β-lactamase appeared, and the strains were susceptible only to imipenem and gentamicin.

Risk factors for* Klebsiella *infection. Potential predisposing factors for *Klebsiella* infection in patients with thalassemia major were examined for the patients treated at Queen Mary Hospital, the teaching hospital of the University of Hong Kong, where a comprehensive electronic clinical database for patients with thalassemia is kept. We examined the age and sex of our patients, as well as the severity of iron overload (the highest ferritin level noted during follow-up) and whether there was a history of splenectomy, because these are important predisposing factors for infection in patients with thalassemia [15]. We also investigated whether the patients had diabetes mellitus or liver derangement (as determined by aspartate aminotransferase level and hepatitis B and C status), to determine the association between these factors and *Klebsiella* infection in other patient groups [16–20]. Only an elevated ferritin level ($P = .046$) and liver derangement ($P = .049$) were found to be marginally significant on univariate analysis. No statistically significant factors could be identified by multivariate logistic regression analysis.

DISCUSSION

The incidence of *Klebsiella* infection among patients with thalassemia major was 0.78 infections per 100 patient-years, and 7.5% of our patients were infected. As determined by a literature search, 5 other Chinese patients who had thalassemia and *Klebsiella* infection have been reported (table 1). According to a review by Wanachiwanawin [15], *Klebsiella* species were responsible for 25% of all severe infections in patients with thalassemia in Thailand. Other important causative organisms in-

Table 1. Data on *Klebsiella* infection in patients with transfusion-dependent thalassemia from the present study and from a literature review.

Patient, case	Sex, age in years[a]	Presenting feature(s)	Diagnosis	Culture specimen	Treatment	Outcome	Reference
1	F, 14	Fever, tender swelling over forehead	Sinusitis, epidural abscess	Surgical	Craniotomy, drainage, antral washout	Recovery	PR
2							
A	M, 21	Right upper quadrant pain	Liver abscess	Surgical	CT-guided aspiration	Recovery	PR
B	22	Left-side neck swelling	Cervical abscess	Surgical	I&D	Recovery	PR
C	29	Headache	Meningitis, septicemia	Blood, CSF	No surgery	Death	PR
3							
A	M, 19	Fever, parotid swelling	Parotid abscess	Blood	No surgery	Recovery	PR
B	20	Headache, changed sensorium	Brain abscess	Surgical	Craniotomy	Residual headache	PR
4	F, 9	Convulsion, vomiting	Brain abscess	Surgical	Craniotomy	Recovery	PR
5	M, 16	Chronic nasal block	Sinusitis	Surgical	Antral washout	Recovery	PR
6	M, 15.5	Right ear pain, right eye swelling	Sinusitis	Surgical	Drainage	Recovery	PR
7	F, 12	Right parotid swelling with fever	Parotitis	Surgical	I&D	Recovery	PR
8	M, 21	Fever and cough after BMT	Recurrent septicemia, pneumonia	Blood[b]	No surgery	Persistent fever	PR
9	M, 12	Fever, vomiting, meningism, impaired sensorium	Subdural empyema	Surgical	Craniotomy	Right-side hemiparesis, epilepsy	PR
10	F, 18.5	Fever, cough	Lung and renal abscess, septicemia	Blood, sputum	No surgery	Recovery	PR
11	M, 11.5	Fever, cough, shock	Pneumonia, septicemia	Blood, sputum	No surgery	Death	PR
12	M, 15.5	Right ear pain and discharge, right eye swelling, headache	Sinusitis, right-side ethmoiditis, right orbital cellulitis, basal ganglia/internal capsule infarct	Surgical	External ethmoidectomy, antral washout	Mild residual left-side hemiparesis	PR
13	M, 19	Precordial heavy sensation, upper arm and shoulder pain	Liver abscess	Surgical	Surgical drainage	Recovery	[11]
14	M, 22	Fever for 1 week, later progression to change of consciousness, vomiting, headache	2 Liver abscesses complicated by right-side pleural effusion, meningitis	Surgical	USG-guided drainage	Recovery	[11]
15	M, 27	Fever, vomiting, confusion	Meningitis with sepsis and DIC	Blood	No surgery	Death	[12]
16	M, 15	Fever, sore throat; later became comatose	Meningitis	Blood, CSF	Craniotomy	Death	[12]
17	F, 14	Fever, decreased breath sounds, left-side postauricular pain, left eye pain, blurred vision	Left-side endogenous endophthalmitis, mastoiditis, pneumonia	Surgical	Anterior chamber irrigation, core vitrectomy, intravitreal antibiotics, dexamethasone	Decreased visual acuity[c]	[13]

NOTE. BMT, bone marrow transplantation; DIC, disseminated intravascular coagulopathy; I&D, incision and drainage; PR, present report; USG, ultrasonography.

[a] Age at the time of presentation.

[b] Culture indicated extended-spectrum β-lactamase in strain.

[c] Patient could not count fingers at a distance of 20 cm.

cluded *Escherichia coli* (26% of infections), *Salmonella* species (15% of infections), and *Streptococcus pneumoniae* (13% of infections).

Yersinia species, however, seem to be a less important cause of infection among patients with thalassemia at our institutions. Since 1991, only 1 of 66 patients observed at Queen Mary Hospital had *Yersinia* infection in the form of cellulitis [21]. Li et al. [6] reviewed the mortality and morbidity patterns for a cohort of 232 patients and found that, of 19 episodes of severe infection, 6 were caused by *Klebsiella* species, whereas only 3 were caused by *Yersinia* species. It is known that *Yersinia* infection tends to occur in cold climates [22] and is relatively rare in tropical areas. We believe that this is just one of the reasons for the low rate of *Yersinia* infection in Hong Kong. This is also evident in Thailand [15], where there is a 10% incidence of *Yersinia* infection among patients with thalassemia major who receive deferoxamine. Of interest, the reports that we could find about *Klebsiella* infection in patients with thalassemia were all from Asia. Whether the paucity of reports of *Klebsiella* infection from places like Mediterranean Europe, where thalassemia is prevalent, is genuine or whether it is because of underreporting needs further investigation.

Another finding worth noting is the high rates of mortality and morbidity associated with *Klebsiella* infection. Two patients (17%) died, and 3 patients (25%) had permanent neurological deficits. This high incidence of complications was not found in the *Yersinia* series by Adamkiewicz et al. [10], but it was observed in the previous case reports of *Klebsiella* infection among patients with thalassemia [11–13], in which 2 patients with meningitis died and 1 patient with endopthalmitis had permanent visual damage.

An attempt was made to identify the risk factors for *Klebsiella* infection in patients with thalassemia major. A high ferritin level and deranged liver function were significant only on univariate analysis. Iron overload was known to be a significant risk factor for *Yersinia* infection in patients with thalassemia major [10, 23]. In laboratory studies, iron was found to be essential for the growth of several bacteria, including *Klebsiella* species [24, 25]. With regard to liver derangement, it can be caused by either iron overload or chronic viral hepatitis. In our series, no patients had hepatitis B infection. Hepatitis C has been shown to be associated with elevated serum alanine aminotransferase levels [26] and more-severe hepatic fibrosis [27]. However, no significant difference was observed in the hepatitis C carrier status between persons who were infected with *Klebsiella* species and those who were not ($P = .07$). Furthermore, no single, independent, significant risk factor could be found by multiple logistic regression analysis, which suggests that multiple interacting risk factors existed and contributed to *Klebsiella* infection in our patients with thalassemia major. A larger patient sample would be necessary to improve the power of the statistical analysis in a future study.

In summary, *Klebsiella* infection was found to be an important complication of thalassemia major in local Chinese patients, both in terms of the incidence and the associated mortality and morbidity rates. Given the poor outcome of infection, prompt treatment (including a sensible choice of antibiotics and early surgical intervention) should be initiated whenever there is suspicion of *Klebsiella* infection. Future studies should be performed to address predisposing factors.

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