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NOTES

Clonorchiasis in Bone Marrow Transplant Recipients

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Among 380 bone marrow transplant (BMT) recipients, five cases (1.3%) of clonorchiasis were observed from 1991 to 1996. *Clonorchis sinensis* infection was evident in the results of stool examinations performed for screening purposes 7 days before bone marrow transplantation. *Salmonella* species were isolated concomitantly from the stools of two of the five patients. None of the patients had symptoms due to clonorchiasis. Ultrasonography did not show dilated hepatobiliary ducts, stones, or periportal fibrosis. Fatty liver changes were detected in one patient. All five patients received praziquantel (25 mg/kg po t.i.d. for 1 day) before bone marrow transplantation. Only two patients who underwent allogeneic transplantation had mild venoocclusive disease of the liver with transient hyperbilirubinemia and mildly elevated liver enzyme levels, whereas hyperbilirubinemia or elevated serum alanine aminotransferase levels, related to conditioning toxicity, occurred in two other patients. After treatment with praziquantel, stool examinations for all five patients were negative for *C. sinensis* ova. In addition, *Salmonella* species were not detected after ciprofloxacin prophylaxis. All five patients survived for >300 days. Given the availability of effective therapy and in the absence of excessive complications, clonorchiasis is not a contraindication to bone marrow transplantation.

Patients who undergo bone marrow transplantation are predisposed to serious bacterial, viral, and fungal infections, most of which have been well studied. However, parasitic infections, especially helminthic diseases, are not encountered frequently among bone marrow transplant (BMT) recipients, since these diseases are more common among patients in developing countries. The most common and important parasites that cause infections in BMT recipients include *Pneumocystis carinii* [1], *Toxoplasma gondii* [2], *Giardia lamblia* [3], microsporidia [4], and *Cryptosporidium parvum* [5]. Infections due to geographically restricted parasites such as *Trypanosoma* [6], *Acanthamoeba* [7], *Plasmodium* [8], *Schistosoma* [9], *Trichostrongylus* [10], and *Strongyloides* [11] may occur occasionally. However, with the inception of more BMT centers in developing countries, as well as the migration of people from developing to developed countries, larger numbers of parasitic infections are anticipated among BMT recipients. It is of interest that among patients with schistosomiasis, periportal fibrosis has been associated with increased risk of venoocclusive disease (VOD) after bone marrow transplantation. Infection due to *Clonorchis sinensis* is endemic in South China. In Hong Kong, 2.2% of the population is infected with this trematode (P.C.Y. Woo, unpublished data). Because patients with serious infections may experience recurrent cholangitis and because there are no reports concerning flares of cholangitis during preparative chemotherapy and subsequent neutropenia among patients who undergo bone marrow transplantation, we report our experience with clonorchiasis among BMT recipients.

Patients and Methods

Data from BMT recipients were recorded systematically during a 6-year period (1991–1996), during which bone marrow transplantation was performed on 380 patients at the Queen Mary Hospital (Hong Kong). The transplantation protocols and antimicrobial and graft-versus-host disease prophylaxis have been described previously [12].

Stool was obtained from all BMT recipients 7 days before the procedure. The specimens were inoculated onto deoxycholate citrate agar and xylose lysine deoxycholate agar for detection of potential gastrointestinal pathogens. In addition, the specimens were concentrated by using the formalin-ether method, and wet mounts were prepared for detection of parasitic ova and cysts. During the patients' transplantation courses, when diarrhea occurred, stool was obtained for detection of potential pathogens, which included wet mounts for detection of parasites. Blood was obtained for cultures when a patient's temperature was >38.5°C and before any change to the antibiotic regimen.

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Blood was obtained for CBC and liver and renal function tests daily until engraftment and then as clinically indicated. Abdominal ultrasonography was performed on all patients with documented clonorchiasis for detection of hepatobiliary and pancreatic abnormalities.

Results

Among 380 BMT recipients, five cases (1.3%) of clonorchiasis were observed (table 1); the median age was 40 years. All patients were hepatitis B surface antigen (HBsAg) negative; three patients were positive for hepatitis B surface antibody (HBsAb) because of previous vaccinations (cases 2, 4, and 5). None of the patients' symptoms were attributable to clonorchiasis. Light microscopic examination (magnification, ×400) revealed light yellow-brown operculated eggs, 29 × 16 μm, with a small median protuberance at the thicker posterior end, characteristic of *C. sinensis* ova, for all five patients undergoing pretransplantation screening. It is of interest that *Salmonella* species were also isolated from two of the five patients (cases 3 and 4). Abdominal ultrasonography revealed fatty liver changes for one patient only (case 5). All five patients received praziquantel (25 mg/kg po t.i.d. for 1 day) before undergoing bone marrow transplantation. None of the patients developed bacteremia. Only two patients who underwent allogeneic transplantation had mild VOD of the liver (cases 1 and 2), with hyperbilirubinemia and mildly elevated liver enzyme levels. After praziquantel treatment, each of the three consecutive subsequent stool examinations for all five patients were negative for *C. sinensis* ova; in addition, *Salmonella* species were not detected after ciprofloxacin prophylaxis. All five patients survived for >300 days.

Discussion

Because bone marrow transplantation is inaccessible in most developing countries, parasitic infections are relatively less frequent than other microbial diseases in BMT recipients. However, international travel and increasing affluence in certain areas of endemicity have resulted in carriers of parasites being donors and recipients of BMTs. In addition to its prevalence among BMT recipients, clonorchiasis is prevalent in our locality. *C. sinensis* ova were detected in the stool samples of five of 380 BMT recipients 7 days before their procedures, with an incidence (1.3%) comparable to that for the general population.

The only report of clonorchiasis in transplant recipients in the literature concerns liver transplantation in our locality [13]. In that report of two cases, adult worms of *C. sinensis* were observed in the donors' livers during organ procurement. Although the parasites were killed by cold perfusion, they caused blockage of the hepatojejunostomy splintage tube and cessation of bile flow during the early postoperative period for one of the recipients.

Clonorchiasis does not appear to be associated with significant complications among BMT recipients; however, because of the small number of infected patients, an extensive analysis of risk factors or outcomes is not possible. Rates of complications such as VOD and mortality for infected patients do not differ significantly from those for noninfected patients. This is in contrast to a series of 89 allogeneic BMT recipients in Egypt, among whom five with schistosomal hepatic periportal fibrosis detected by pretransplantation ultrasonography died of severe VOD despite initial normal liver function and absence of portal hypertension [9]. Because there was no evidence of periportal fibrosis in our patients, it is not surprising that the incidence of VOD was comparable to that for uninfected BMT recipients.

Table 1. Characteristics of five bone marrow transplant recipients with clonorchiasis.

	Case no.				
Characteristic	1	2	3	4	5
Gender/age (y)	M/47	F/37	F/42	F/40	F/38
Underlying disease	CML-CP	AML-CR1	Breast cancer	CML-CP	Breast cancer
Transplantation type	Allogeneic	Allogeneic	Autologous, PSC	Allogeneic	Autologous
Conditioning	Bu/Cy	Bu/Cy	Carboplatin, VP-16, Cy	Bu/Cy	Carboplatin, VP-16, Cy
Engraftment (d)	31*	17	10	28	28
GVHD prophylaxis	Mtx, Cysp	Mtx, Cysp	None	Mtx, Cysp	None
Highest serum bilirubin level in μmol/L (d)†	109 (12)	68 (12)	31 (−3)	<19	<19
Highest serum ALT level in U/L (d)†	36 (12)	151 (8)	<31	<31	111 (2)
Highest serum ALP level in U/L (d)†	<138	194 (21)	<104	<104	<104

NOTE. ALP = alkaline phosphatase; ALT = alanine aminotransferase; AML = acute myeloid leukemia; Bu = busulphan; CML = chronic myeloid leukemia; CP = chronic phase; CR = complete remission; Cy = cyclophosphamide; Cysp = cyclosporine; GVHD = graft-versus-host disease; Mtx = methotrexate; PSC = peripheral stem cell; VP-16 = etoposide.

* Engraftment after administration of growth factors.

† Normal ranges: total serum bilirubin, 7–19 μmol/L; ALT, 6–53 U/L (male) and 5–31 U/L (female); ALP, 49–138 U/L (male) and 34–104 U/L (female).

The association of clonorchiasis with cholangiocarcinoma and recurrent pyogenic cholangitis in areas of endemicity was not evident among our BMT recipients, and throughout the course of transplantation none of them had bacteremia. *C. sinensis* initiates inflammatory and proliferative reactions in the biliary epithelium with which the parasite makes contact, leading to encapsulating fibrosis of the ducts. Repeated exposure to *C. sinensis* in distal bile passages provokes considerable local tissue reaction as a result of mechanical irritation and toxic products, formation of new bile capillaries, mucinous glands and periportal connective tissue hyperplasia, and periepithelial fibrosis. In addition, there is colonization of bile by bacteria predisposing to cholangitis and bacteremia. These complications are progressive, and their ultimate effect on liver function depends on the number of worms present and the duration of the infection, which may be ⩾20 years for humans. However, with improvements in public health measures over the past few decades, the prevalence of clonorchiasis and the worm burden has gradually decreased. Currently, most patients with clonorchiasis are infected only mildly. Therefore, it is likely that hepatobiliary damage seen in younger individuals will be less severe than that in older individuals. Although all five patients with clonorchiasis were significantly older than the median age of 32 for our BMT recipients, ultrasonography for these infected patients did not reveal stones, dilated ducts, or other obstructive features characteristic of chronic clonorchiasis.

It is unlikely that severe luminal helminthic infection will become a major problem among BMT recipients, although increasing numbers of bone marrow transplantations are anticipated in areas of endemicity. Luminal helminths such as *C. sinensis* lack a tissue-invasive phase (as opposed to helminths such as *Trichostrongylus* species) or a latent stage in human hosts (as opposed to other parasites such as *Leishmania* and *Toxoplasma* species, which might be reactivated during profound suppression of cell-mediated immunity). In addition, *C. sinensis* does not multiply within the body. This finding is in contrast to that for parasites such as most protozoa or *Strongyloides* species, which are well known to cause autoinfection. In addition, pretransplantation praziquantel treatment will almost certainly destroy all the adult worms and lessen complications during transplantation.

Concomitant carriage of *Salmonella* species was noted for two of the five BMT recipients with clonorchiasis. It is well known that a higher incidence of chronic *Salmonella* carriage occurs among individuals with nidi in the biliary tree and among immunocompromised patients. Because all BMT recipients had severe underlying disease, and *C. sinensis* adult worms can act as nidi for *Salmonella* species, it is not surprising that BMT recipients with clonorchiasis had a higher rate of *Salmonella* carriage.

Although the host defense against *C. sinensis* is not completely understood, in the absence of solid evidence concerning the adverse effects of immunosuppression on the clinical course of clonorchiasis, low worm burdens in the general population, and with the availability of effective antihelminthic agents, clonorchiasis is not a contraindication to bone marrow transplantation, and no excessive complications are expected.

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