Immunorestitution Diseases in Non-HIV Infected Patients

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Abstract. The aim of the study is to assess the clinical spectrum of immunorestitution disease (IRD) in hospitalised patients over a 12-month period. In 9 of 18 patients who presented with clinical deterioration during reduction or cessation of immunosuppressants (n=6) or bone marrow engraftment (n=3), IRD cases included scabies infestation (n=1), gastric strongyloidiasis (n=1), hepatosplenic candidiasis (n=1), methicillin-resistant *Staphylococcus aureus* abscess formation (n=2), polyomavirus-related hemorrhagic cystitis (n=3), and influenza A pneumonitis (n=1). Immunopathological damage during withdrawal of immunosuppression is an incidental way to uncover an asymptomatic infectious disease. Serial monitoring of hematological and clinical profiles are essential in making a diagnosis of IRD.

Introduction

The initial concept of immunorestitution disease (IRD) was enlightened by the observation of the onset of symptomatic expression or paradoxical deterioration of pre-existing infectious diseases, including cytomegalovirus retinitis, pulmonary or extrapulmonary tuberculosis, atypical mycobacterial lymphadenitis, and cryptococcal infection, in HIV-positive patients with a recovery of $CD4^+$ lymphocyte counts after initiation of highly active antiretroviral therapy (HAART) [1]. However, the encompassing concept of IRD involving innate and adaptive immunity was subsequently formulated with the observation of a similar phenomenon in non-HIV immunosuppressed patients with opportunistic infections after dosage reduction or withdrawal of steroid, recovery of absolute neutrophil count (ANC) from cytotoxic therapy, or engraftment after bone marrow transplantation (BMT) [2]. Despite these reports, the true incidence and the clinical spectrum of IRD in daily practice have not been documented. The unawareness of clinicians about this emerging disease entity, the nonspecific clinical signs and symptoms, and the lack of a standard diagnostic laboratory test are all factors that hinder the understanding of this disease. Therefore, a prospective study was conducted to evaluate the extent to which IRDs are encountered in our inpatient consultative service.

Materials and Methods

Data were collected prospectively over a 12-month period (January 1999 - December 1999) on patients referred for infectious disease (ID) consultation in a tertiary hospital (Queen Mary Hospital, Hong Kong, a 1,350-bed teaching hospital). For the purpose of this study, patients who had received immunosuppressive therapy (systemic steroid, cytotoxic agents, or combination of steroid and cytotoxic agents) or undergone BMT (conditioning regimen including cytotoxic and/or total body irradiation), resulting in an ANC of less than 500/μl or an absolute lymphocyte count (ALC) of less than 1500/μl were defined as immunosuppressed hosts. IRD is defined as an acute symptomatic illness or paradoxical deterioration of a (presumably) pre-existing infection, which is temporally related to the recovery of the immune system and which is due to immunopathological damage associated with one of the following: (i) the reversal of immunosuppressive processes such as withdrawal of steroid, (ii) recovery of the ANC from chemotherapy, or (iii) engraftment after BMT. The pre-existing microbial infection could be either asymptomatic or mildly symptomatic.

The handling procedure for consultations has been described previously [3, 4]. Besides detailed history and physical examination, case notes review, the dosing regimen of immunosuppressive therapy, and the exact timing of dosage reduction or withdrawal of immunosuppressants were noted in immunosuppressed patients. The time interval between reduction or withdrawal of immunosuppressive therapy, recovery of ANC after cytotoxic agents, or engraftment after BMT and onset of clinical symptoms of IRD were recorded.

Results and Discussion

In this prospective study, there were 2,225 inpatient ID consultations over the study period, of which 280 (12.6%) patients with median age of 45, ranged 1-83, were receiving immunosuppressive therapy. Eighteen (6.4%) patients had onset of or worsening of clinical symptoms and signs when the doses of immunosuppressants were being reduced or the drugs withdrawn. IRD was documented in 9 (50%) of these patients. The clinical details of these cases are listed in table 1.

Case 1 was a 12-year-old boy presented with pruritic lesions over the external genitalia 4 days after the engraftment of neutrophil following allogeneic BMT for his dyskeratosis congenita. He developed neutropenic fever and was put on empirical intravenous ceftazidime and amikacin. He engrafted on day 13 with a total leukocyte count of 1,630/µl, ANC 880/µl, ALC 390/µl and AMC 260/µl. During the postengraftment period, his ANC progressively increased from 880/µl to 4,450/µl and AMC from 260/µl to 1,410/µl on day 13 to 16 respectively. On day 17, while the ANC was 2,140/µl and AMC was 1,020/µl, he was noted to have multiple pruritic erythematous nodules over the penis and scrotum. Skin biopsy on day 21 demonstrated nonspecific histiocytic aggregation and lymphoplasmacytic infiltration in dermal and epidermal layers but there was no apoptotic bodies suggestive of cutaneous GVHD. Wet mount of the skin scraping confirmed the presence of *Sarcoptes scabiei*. A diagnosis of postengraftment scabies was made. He was treated with a standard regimen of topical benzyl benzoate for 2 days with satisfactory clinical improvement. Contact tracing of the family members revealed that his

younger brother, who used to sleep with the patient, also suffered from the same disease three weeks before the patient underwent BMT.

Case 2 was a 42-year-old woman with a history of lupus nephritis receiving long-term steroid and azathioprine, admitted for surgical management of necrotizing fasciitis of her right lower limb. She improved after radical surgical debridement and a combination of intravenous antibiotic therapy including amoxicillin-clavulanate and ofloxacin. During the convalescent phase, the dose of prednisolone was reduced from 60 mg qd to 15 mg qd over 29 days while the AEC increased from 30/μl to 1,100/μl and ALC increased from 560/μl to 1,800/μl respectively. While the AEC and ALC levels were highest, she developed severe epigastric, cramping abdominal pain and diarrhea. Upper endoscopy showed evidence of antral gastritis and duodenitis. Antral biopsy demonstrated multiple *Strongyloides* larvae in the gastric mucosa with inflammatory and eosinophilic infiltration. IRD due to pre-existing gastric strongyloidiasis upon withdrawal of steroid was diagnosed and she was treated with oral albendazole 400 mg qd for 7 days.

Case 7 was a 39-year-old man receiving high dose cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy) as preconditioning therapy for autologous BMT for diffuse large cell lymphoma (stage 1A). He had an uneventful course during the pre-engraftment phase. Surveillance cultures including surface swabs, urine culture, stool culture, and blood culture were taken on day 0, 7, 14 and weekly onwards for microbiological examination. Asymptomatic shedding of polyomavirus was detected in the urine on days 14 and 21 when the corresponding ALC were 0 and 300/μl respectively. Electron microscopy (EM) showed the presence of numerous non-

enveloped virus particles of 40 nm in diameter inside the intranuclear inclusion bearing cells. Cytological examination of urine demonstrated scattered, large atypical cells, which were round and spindle-shaped with a high nuclear / cytoplasmic ratio in both Sterheimer-Malbin staining and Papanicolaou staining. The bone marrow engrafted on day 24, when the total leukocyte count was 2,100/μl, ANC 600/μl and ALC 1,100/μl. On the same day, he developed symptomatic hemorrhage cystitis with worsening of dysuria and increasing hematuria. Repeated EM examination of urine on day 28 was negative for polyomavirus. He was treated with IVIG for 3 days and the symptoms subsided on day 34 while the ALC dropped to 400/μl.

As shown in the illustrative cases, besides the worsening of underlying diseases, development of antimicrobial resistance, and other noninfectious complications, IRD should be considered as an important differential diagnosis in this particular group of patients.

A broad spectrum of microorganisms have been identified in patients with IRD, including parasites, fungi, mycobacteria, bacteria and viruses. Systemic mycobacterial and fungal infection in the setting of IRD had been discussed in detail in our previous study [2]. The ectoparasite, *Sarcoptes scabiei*, is first documented as a manifestation of IRD in the present study. Similar observations to those in our patient have previously been reported in a 4-year-old boy undergoing BMT for acute lymphoblastic leukemia [5]. However, the authors did not report the case from the perspective of IRD and the lack of serial hematological profiles made documentation of IRD impossible. A severe form of scabies, called Norwegian or crusted scabies, has been reported in solid organ transplant recipients and AIDS patients [6, 7]. It is

characterized by widely distributed psoriasis-like hyperkeratotic crusted nodules and plaques. Although the number of viable mites found on a single patient could be thousands or even millions, there is far less pruritis and frank inflammation is often lacking. The clinical manifestations of scabies depend on the host immunity, as supported by a previous study in which skin was injected intradermally with *Sarcoptes* extracts in an immunocompetent host. Mononuclear cellular infiltration was detected by serial histological sectioning [8].

Human strongyloidiasis was also associated with IRD in this study. Strongyloides infection is normally checked by cell-mediated immunity with predominantly T-helper type two response resulting in eosinophilia. Overwhelming infection in terms of massive invasion of the gastrointestinal tract and pulmonary tissue may occur in patients with defective T lymphocyte function [9, 10]. Our patient survived the infection during the immunosuppressive phase with few symptoms but developed IRD manifesting as abdominal pain and diarrhea after reduction of the dose of steroid. Recovery of the immune system was evidenced by progressive rise in ALC and AEC. The occurrence of immunopathological damage during withdrawal of immunosuppressive therapy or bone marrow engraftment, as exemplified in parasitic infestations, is an incidental way to uncover an undiagnosed asymptomatic infectious disease in patients with underlying disease which require immunosuppression.

Pyogenic bacterial infections are also associated with IRD. Previously, we hypothesized that IRD would be confined to patients infected by slow growing pathogens of low virulence. In actual fact, IRD can also be observed in pyogenic bacterial infection in tissues where antibiotic penetration is problematic. Patient 5

developed pyomyositis following an episode of catheter-related MRSA bacteremia. We postulate that the occurrence of pyomyositis was secondary to the metastatic deposit of the organism to a microhematoma inside the calf muscle. The microhematoma provided an environment for bacterial multiplication and protection from antibiotic killing. During the neutropenic phase, he had nonspecific cramping in the affected area. Subsequently, during immunorestitution, erythema and swelling developed, and evolved to a firm, hard or woody mass. Later the infiltration of neutrophils produced an area of fluctuance and aspiration at this stage yielded purulent material.

As for viral infection, polyomavirus-related hemorrhagic cystitis in BMT recipients after reduction of steroid in the treatment of GVHD or after engraftment constituted 33% of cases in the present study. Reactivation of latent polyomavirus due to impairment of cell mediated immunity has been demonstrated as one of the etiological factors for hemorrhagic cystitis in seropositive patients undergoing BMT. The occurrence of disease correlated with viruria and the shedding of virus could precede or coincide with the onset of cystitis [11, 12]. However, the incidence of hemorrhagic cystitis following withdrawal of immunosuppressants or bone marrow engraftment has not been investigated in previous studies [11, 12]. In patient 7, we clearly demonstrated asymptomatic shedding of polyomavirus during the pre-engraftment or immunosuppressive phase. The patients developed symptomatic hemorrhagic cystitis after recovery of the immune system as evidenced by the concomitant increase in ALC either by marrow engraftment or rapid dosage reduction of steroid. Therefore, besides cytolytic damage during immunosuppression, the

immunopathological manifestation of polyomavirus-related hemorrhagic cystitis should also be considered as an IRD in certain setting. However, the bleeding diathesis limited our assessment of the histological changes in the urinary bladder during immunosuppression and IRD. In renal transplant recipients, cytopathic changes with nuclear enlargement, irregularity of nuclear contour, and clumping and smudging of chromatin pattern are the predominant lesions of polyomavirus infection during immunosuppression. Extensive interstitial inflammation by mononuclear cells and plasma cells may occur in the phase of immunorestitution resulting in immunopathological damage [13, 14]. This may explain why polyomavirus is not detected in urine during symptomatic cystitis. The use of IVIG therapy as an effective immunomodulating agent to control the overwhelming inflammatory response during immunorestitution was anecdotally associated with a decrease in the duration of symptoms by 7 to 10 days in our patients.

In view of the wide spectrum of pathogens involving different organ systems, ID specialists should be vigilant in considering this new diagnostic entity. In the assessment of any immunosuppressed patient with suspected infection, careful review of the regimen of immunosuppressive therapy, close monitoring of serial hematological profiles, and detailed analysis of signs and symptoms before and during immune recovery are crucial in diagnosing IRD. New information will be generated as more cases of IRD are identified. With a better understanding of this disease, prophylactic, preemptive and therapeutic regimens for IRD could be established.

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Table 1. Immunorestitution disease (IRD) encountered in infectious disease consultation

Case no.	Sex / age	Underlying diseases / IS therapy	Infecting organisms/ sites/ details of recovery of immune system	Duration between recovery of immune system and onset of IRD	Cell counts before IRD (/μlL)	Cell counts during IRD (/μlL)	Symptoms and signs of IRD	Treatment of IRD in addition to anti-microbial therapy
1	M/12	dyskeratosis congenita; allogeneic BMT	*Sarcoptes scabiei* involving external genitalia after engraftment of marrow	4 days	AMC 260; ANC <500	AMC 1020; ANC 2140	multiple pruritic erythematous nodules in penile and scrotum	Nil
2	F/42	SLE; on high dose steroid	*Strongyloides* involving stomach after dosage reduction of prednisolone 60mg qd to 15mg qd over 29 days	29 days	AEC 30; ALC 560	AEC 1100; ALC 1800	abdominal pain and diarrhoea; antral biopsy showed numerous *Strongyloides*	Nil
3	F/22	ALL; consolidation chemotherapy	HSC after recovery of ANC	20 days	ANC <500	ANC 10600	recurrent fever; right upper quadrant pain and increasing ALP	Nil
4	M/38	AML; induction chemotherapy	MRSA abscess of buccal mucosa after recovery of ANC[a]	3 days	ANC 100	ANC 700	left facial swelling and tenderness	Nil
5	M/38	AML; consolidation chemotherapy	MRSA pyomyositis of both calf after recovery of ANC[a]	3 days	ANC <500	ANC 1700	severe calf tenderness with abscess formation	Nil

6	M/31	CML; allogeneic BMT; high dose steroid for graft-versus-host-disease	polyomavirus -related HC at day 94 after dosage reduction of prednisolone from 60mg qd to 30mg qd over 8 days	8 days	ALC 400	ALC 1010	dysuria and hematuria	IVIG
7	M/39	NHL; autologous BMT	polyomavirus -related HC at day 24 after engraftment of marrow	0 day	ALC 300	ALC 1100	dysuria and hematuria	IVIG
8	F/8	beta-thalassemia / hemoglobin E transfusion dependent syndrome; allogeneic BMT; high dose steroid for graft-versus-host disease	Polyomavirus -related HC at day 71 after dosage reduction of methyl-prednisolone from 100mg qd to 30mg qd over 20 days	20 days	ALC 70	ALC 600	dysuria and hematuria	Nil
9	M/39	NHL; autologous BMT	influenza A (H3N2) pneumonitis after engraftment of marrow[b]	0 day	ALC 100	ALC 1100	acute onset of shortness of breath; CXR showed extensive infiltrative lesions	IVIG

[a] MRSA bacteremia was documented before the recovery of ANC
[b] Influenza A (H3N2) was documented in nasopharyngeal aspirates by direct antigen detection and viral culture before bone marrow engraftment

AEC, absolute eosinophil count; ALC, absolute lymphocyte count; ALL, acute lymphoblastic leukemia; ALP, alkaline phosphatase; AMC, absolute monocyte count; AML, acute myeloid leukemia; ANC, absolute neutrophil count; BMT = bone marrow transplantation; CML = chronic myeloid leukemia; CXR = chest radiography; HC, hemorrhagic cystitis; HSC, hepatosplenic candidiasis; IRD, immunorestitution disease; IS, immunosuppressive; IVIG, intravenous immunoglobulin; MRSA, methicillin-resistant *Staphylococcus aureus*; NHL, non-Hodgkin lymphoma; SLE, systemic lupus erythematosus.