Value of serum C-reactive protein measurement in the management of bone marrow transplant recipients. Part II: late post-transplant period

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SUMMARY Seventeen bone marrow recipients transplanted for acute leukaemia (8), chronic leukaemia (1), severe aplastic anaemia (3), and various inborn errors of metabolism (5) had 22 episodes of documented infection in the late (>3 months) post-transplant period. Serum C-reactive protein concentrations were considerably increased in patients with bacterial infections, but not in those with viral or fungal infections.

Serum C-reactive protein values were normal in 20 patients transplanted for acute leukaemia (12), chronic leukaemia (1), severe aplastic anaemia (2), and various inborn errors of metabolism (5) who had active chronic graft versus host disease but no evidence of infection. These findings indicate that serum C-reactive protein concentrations are useful in the diagnosis and monitoring of bacterial infections even in the presence of chronic graft versus host disease.

Late infections are arbitrarily defined as those occurring later than three months after transplant. Most of these infections are bacterial,¹ with an unexpectedly high incidence of serious or fatal pneumococcal disease²; they occur more often in bone marrow transplant recipients with active chronic graft versus host disease.³ Chronic graft versus host disease occurs in about 30% of long term survivors of bone marrow transplantation⁴ and is related to a wide range of cellular and humoral immunological abnormalities.⁵⁻⁷ This immune imbalance predisposes patients to infection, contributing to morbidity and mortality in the late post-transplant period.

HLA non-identical transplants are associated with an increased risk of late infections,¹ and the use of the selective immunosuppressant cyclosporin A can be expected to increase the number of such transplants performed.

There is an obvious place for any laboratory test which could be used in the diagnosis and monitoring of bacterial infections to help improve long term survival. In the early transplant period the acute phase reactant C-reactive protein (CRP) is of value

because raised serum concentrations are associated predominantly with bacterial infections and not acute graft versus host disease⁸; but the nature of the acute phase response in chronic graft versus host disease has not been investigated.

We have analysed the serum CRP concentrations found in bone marrow transplant recipients in relation to documented infection and chronic graft versus host disease in the late post-transplant period.

Patients and methods

Serum CRP concentrations were measured as described previously⁸ on samples taken regularly from bone marrow transplant recipients admitted with suspected or proved infections in the late post-transplant period.

There were 22 clearly documented episodes of infection in 17 patients transplanted for acute leukaemia (8), chronic leukaemia (1), severe aplastic anaemia (3), and various inborn errors of metabolism (5).

CRP concentrations were also measured in serum samples taken in the outpatient clinic from 20 patients transplanted for acute leukaemia (12), chronic leukaemia (1), severe aplastic anaemia (2),

Maximum serum C-reactive protein (CRP) concentrations in bone marrow transplant recipients later than three months after transplant.

Bacterial infection: I = microbiologically documented septicaemia; II = clinically documented infection; III = microbiologically documented localised infection.

Horizontal bar indicates median serum CRP concentration for each group.

and various inborn errors of metabolism (5) who had active chronic graft versus host disease diagnosed clinically and histologically⁹ but no evidence of infection.

Results

Patients were grouped according to the type of infection (bacterial, viral, fungal, or mixed). The sites and causative agents (where known) of these infections are shown in Tables 8 and 9 (see appendix), together with the time after transplant and whether or not active chronic graft versus host disease was present.

The maximum serum CRP concentrations reached during each episode of infection are shown in the Figure, together with the serum CRP concentrations in patients with active chronic graft versus host disease without infection and the median CRP value for each patient group. Statistical comparisons were not possible because of the small numbers of patients in some groups. It is quite clear, however, that considerably raised serum CRP concentrations were seen exclusively in association with bacterial infections.

Discussion

This study has shown that chronic graft versus host disease is not accompanied by increased serum concentrations of the acute phase protein CRP as none of the patients in the group had values above 10 mg/l, the arbitrary upper limit of normal in our laboratory.¹⁰ CRP is one of the most sensitive markers of the acute phase response, and in many chronic inflammatory conditions—for example, rheumatoid arthritis, rheumatic fever, Crohn's disease, and familial mediterranean fever—serum concentrations are increased during the active phase of the disease. But in others, such as systemic lupus erythematosus, scleroderma, and mixed connective tissue disease, serum concentrations are normal or only slightly increased in active disease.¹¹ The lack of a CRP response in patients with active chronic graft versus host disease is therefore not unique. These patients, like those with systemic lupus erythematosus, are able to mount the expected CRP response to bacterial infections.

Viral and fungus infections were associated with normal serum CRP values, as seen previously in the early transplant period.⁸

In conclusion, a raised serum CRP concentration is as sensitive a marker for the diagnosis and monitoring of bacterial infections in bone marrow transplant recipients in the late transplant period as it is in the early transplant period.⁸

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Appendix

Table 1 Microbiologically documented septicaemia in the early transplant period

No of episodes	Causative organism(s)
1	Faecal streptococcus
2	<i>Streptococcus mitis</i>
2	<i>Pseudomonas aeruginosa</i>
2	<i>Klebsiella oxytoca</i>
6	<i>Staphylococcus epidermidis</i>
1	{ <i>Staph epidermidis</i> <i>Staph aureus</i>

Table 2 Microbiologically documented localised infections (negative blood culture) in early transplant period

Organism(s)	Associated infection(s)
<i>Pseudomonas aeruginosa</i>	Hickman catheter entry site
<i>Ps aeruginosa</i>	Mediastinal abscess
<i>Escherichia coli</i>	Urinary tract
<i>Streptococcus pneumoniae</i>	Upper respiratory tract (2)
<i>Viridans streptococcus</i> *	Pneumonia
<i>Staphylococcus epidermidis</i>	Cellulitis of foot
<i>Staph epidermidis</i>	Hickman catheter entry site (2)
<i>Staph aureus</i>	Abscess on arm
<i>Str pneumoniae</i>	Otitis media
<i>Haemophilus influenzae</i>	
<i>Faecal streptococcus</i>	
<i>Staph epidermidis</i>	Hickman catheter entry site
<i>Klebsiella oxytoca</i>	Hickman catheter entry site
<i>Staph epidermidis</i>	

*Importance uncertain.

Numbers in parentheses = numbers of patients.

Table 3 Clinically documented infection (negative bacteriology) in the early transplant period

Infection	Outcome
Pyogenic abscess at lumbar puncture site	Responded to laminectomy and drainage
Pneumonia	Good response to antibiotics
Cellulitis with abscess over left zygoma	Patient died after initial response to antibiotics
Pneumonia and septicaemia	Clinical evidence only. Patient died

Table 4 Viral infections in the early transplant period

Agent(s)	Associated infection(s)
Rotavirus	Gastroenteritis (3)
Herpes simplex virus	Mucositis (3)
Non A, non B hepatitis virus	Hepatitis
Calicivirus	Gastroenteritis
Varicella-zoster	Chickenpox
Cytomegalovirus	Pneumonia; gastroenteritis; pharyngitis
Adenovirus	
Herpes simplex virus	
Parainfluenza	Pneumonia; conjunctivitis
Adenovirus	

Numbers in parentheses = numbers of patients.

Table 5 Fungal infections in the early transplant period

Agent(s)	Associated infection(s)
<i>Candida albicans</i>	Mucositis (2)
<i>Cand albicans</i>	Gastrointestinal
<i>Cand albicans</i>	Hickman catheter entry site
<i>Aspergillus fumigatus</i>	Sinusitis
<i>Asp fumigatus</i>	Systemic mycosis
<i>Cand albicans</i>	

Number in parentheses = number of patients.

Table 6 Mixed infections in the early transplant period

Agent(s)	Associated infection(s)
<i>Serratia</i> spp	Septicaemia; pneumonia
Cytomegalovirus	
<i>Staphylococcus epidermidis</i>	Septicaemia; pneumonia
Respiratory virus*	
<i>Staph epidermidis</i>	Hickman catheter entry site; mucositis
Herpes simplex virus	
<i>Staph aureus</i>	Vesicles on dorsal trunk
Herpes simplex virus	
Viridans streptococcus†	Upper respiratory tract infection; vesicles on jaw
Varicella-zoster	
Faecal streptococcus	Urinary tract infection; mucositis
<i>Candida albicans</i>	
<i>Enterobacter cloacae</i>	Urinary tract infection; gastroenteritis
Rotavirus	
Herpes simplex virus	Mucositis; gastrointestinal
<i>Cand albicans</i>	
Herpes simplex virus	Mucositis; gastrointestinal
<i>Giardia lamblia</i>	
<i>Cand albicans</i>	

*Viral infection indicated by histology at necropsy.

†Importance uncertain.

Table 7 Infections occurring concomitantly with acute graft versus host disease in the early transplant period

Agent(s)	Associated infection(s)
<i>Streptococcus</i> spp	Septicaemia (5)
<i>Staphylococcus epidermidis</i>	Septicaemia
<i>Staph epidermidis</i>	Hickman catheter entry site
<i>Staph epidermidis</i>	Septicaemia
<i>Proteus mirabilis</i>	
<i>Staph epidermidis</i>	Septicaemia
Faecal streptococcus	Urinary tract infection
<i>Staph epidermidis</i>	Septicaemia
BCG	BCGosis
<i>Enterobacter cloacae</i>	Septicaemia
BCG	BCGosis
<i>Pseudomonas aeruginosa</i>	Septicaemia
Unknown—responded to antibiotics	Upper respiratory tract infection (2)
Unknown—responded to antibiotics	Hickman catheter entry site
Unknown—responded to antibiotics	Septicaemia
Faecal streptococcus	Bacteraemia; mucositis
<i>Candida albicans</i>	
<i>Staph epidermidis</i>	Septicaemia; mucositis (2)
<i>Cand albicans</i>	
Herpes simplex virus	Urinary tract infection, mucositis
<i>Pseudomonas aeruginosa</i>	
Herpes simplex virus	Pharyngitis (2)
Herpes simplex virus	Gastroenteritis (3)
Rotavirus	Electroencephalogram consistent with encephalitis
Varicella-zoster	Mucositis
<i>Cand albicans</i>	

Numbers in parentheses = numbers of patients.

Table 8 Bacterial infections in the late post-transplant period

Organism(s)	Associated infection	Months after transplant	Active chronic graft versus host disease
<i>Bacteroides fragilis</i>	Septicaemia	17	Present
<i>Enterobacter cloacae</i>	Pneumonia/septicaemia	25	Absent
<i>Staphylococcus aureus</i>	Septicaemia	37	Absent
<i>Streptococcus pneumoniae</i>	Pneumonia/septicaemia	6	Present
Viridans streptococcus	Septicaemia	29	Present
<i>Str pneumoniae</i>	Pneumonia	5	Present
<i>Str pneumoniae</i>	Pneumonia	9	Present
<i>Str pneumoniae</i>	Pneumonia	12	Absent
<i>Haemophilus influenzae</i>	Pneumonia	12	Present
<i>Staph aureus</i>	Pneumonia	84	Absent
<i>Staph epidermidis</i> *	Pneumonia	24	Absent
Unknown—responded to antibiotics	Pneumonia	10	Absent
Unknown—responded to antibiotics	Pneumonia	5	Present
Unknown—responded to antibiotics	Upper respiratory tract	12	Absent

*Importance uncertain.

Table 9 *Viral, fungal, and mixed infections in the late post-transplant period*

<i>Agent(s)</i>	<i>Associated infection(s)</i>	<i>Months after transplant</i>	<i>Active chronic graft versus host disease</i>
Hepatitis B virus	Hepatitis	5	Present
Varicella-zoster	Chickenpox	3	Present
Varicella-zoster	Rash on thigh	4	Absent
<i>Candida albicans</i>	Brain abscesses	20	Absent
<i>Cand albicans</i>	Mucositis	12	Absent
<i>Streptococcus pneumoniae</i> }	Pneumonia/septicaemia; mucositis	4	Present
<i>Cand albicans</i>			
<i>Pseudomonas aeruginosa</i> }	Pneumonia/septicaemia; mucositis; enteritis	6	Present
<i>Cand albicans</i>			
Enterovirus	Pneumonia; mucositis	26	Present
Coliforms*			
<i>Cand albicans</i> }			
Herpes simplex virus }			

*Importance uncertain.