Serum $\beta_2$-microglobulin and C reactive protein concentrations in viral infections

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SUMMARY Serum $\beta_2$-microglobulin concentrations were assayed in a number of virus diseases. Infectious mononucleosis, cytomegalovirus, and influenza A were associated with pronounced increases in serum $\beta_2$-microglobulin concentration. Smaller increases, with values generally $<4$ mg/l, were noted in other viral infections. Apart from in acute influenza A, the C reactive protein and $\beta_2$-microglobulin responses were not associated.

$\beta_2$-microglobulin is a low molecular weight protein (11-8 kilodaltons) that forms the light chain of the major histocompatibility antigens (HLA, A, B, C). $\beta_2$-microglobulin in the serum is derived from HLA turnover and shows little day to day variation in its concentration in healthy individuals. Serum $\beta_2$-microglobulin values tend to increase with age owing to a gradual reduction of the efficiency of its clearance from the blood by glomerular filtration.1

There have been several reports of increased concentrations of serum $\beta_2$-microglobulin associated with acute infectious mononucleosis.2,3 A more detailed investigation of this phenomenon by Lamelin et al.4 led to the suggestion that the serum $\beta_2$-microglobulin concentrations may provide a global estimate of T cell activation in vivo, reflecting the activity of subsets of lymphocytes that do not necessarily enter the peripheral blood. High concentrations of serum $\beta_2$-microglobulin have also been found in cytomegalovirus infection in patients with kidney transplants with normal serum creatinine values.5 Similar increases in serum $\beta_2$-microglobulin have also been described in cytomegalovirus infection after bone marrow grafts6 and cardiac transplantation.7

We report a preliminary survey of the serum $\beta_2$-microglobulin concentrations found in several common forms of virus infection, including an outbreak of influenza A. The serum $\beta_2$-microglobulin concentrations have been compared with the serum C reactive protein response. The results emphasise the problems that may be encountered when trying to interpret the reason for a change in serum $\beta_2$-microglobulin concentration in diseases that disturb the balance of lymphocyte subsets and increase the patient’s susceptibility to viral infections.

Material and methods

SERUM SAMPLES

One hundred and fifty eight serum samples were studied, which were mainly from the serum bank of the virology department of the Public Health Laboratory in Leeds. The samples had been stored at $-20^\circ$C after routine investigations to establish the likely cause of the patient’s infection. Additional samples from patients with cytomegalovirus infections with normal serum creatinine concentrations and without any immunosuppressive disease were kindly provided by Dr Torsten Sandberg, Department of Infectious Diseases, University of Gottenberg. Except for infectious mononucleosis samples and some of the cytomegalovirus samples, pairs of sera from each patient were tested; these were the presentation sample and a convalescent sample taken 7–21 days later. Serum creatinine measurements on patients with other viral diseases were not available; insufficient serum was available to allow us to make the measurements. Two groups of patients whose serum samples were sent for virological examination but who did not have virus infections were also examined. They included 10 patients with suspected infectious mononucleosis whose antibody titres were not raised and 11 patients with Mycoplasma pneumoniae infection.

PROTEIN ANALYSIS

Serum $\beta_2$-microglobulin concentrations were measured in duplicate by a radioimmunoassay using the Phadebas $\beta_2$-micro test 100 (Pharmacia Diagnostics...
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AB, Uppsala, Sweden). The mean and upper limit of normal (+2 SD) of serum $\beta_2$-microglobulin in normal subjects under the age of 60 are 1.7 and 2.6 mg/l, respectively, and in subjects over the age of 60 are 2.0 and 3.1 mg/l, respectively. The ranges were calculated from blood donors and healthy subjects examined in our laboratory during 1977–1984 and agree with the kit manufacturer’s recommendations.

Serum $\beta_2$-microglobulin was measured by radial immunodiffusion using antisera and standards obtained from Behringwerke, Marburg/Lahn, Germany.

Results

$\beta_2$-MICROGLOBULIN

Fig. 1 shows the distribution of serum $\beta_2$-microglobulin concentrations in the presentation

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Serum $\beta_2$-microglobulin concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
</tr>
<tr>
<td>Normal (age &lt;60 yr)</td>
<td>1.7 ± 0.45</td>
</tr>
<tr>
<td>Infectious mononucleosis (Epstein-Barr virus)</td>
<td>4.8 ± 1.7</td>
</tr>
<tr>
<td>(8 convalescent)</td>
<td></td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>Influenza A</td>
<td>4.2 ± 1.9</td>
</tr>
<tr>
<td>Influenza B</td>
<td>2.3 ± 0.6</td>
</tr>
<tr>
<td>Rubella</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>2.0 ± 0.8</td>
</tr>
<tr>
<td>Measles</td>
<td>3.6</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>2.3</td>
</tr>
<tr>
<td>Measles</td>
<td>2.3</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>2.7 ± 0.5</td>
</tr>
</tbody>
</table>

Values given as mean ± SD.
serum samples from patients with virus infections. The means and standard deviations of the serum $\beta_2$-microglobulin concentrations in virus infections are given in the Table. $\beta_2$-microglobulin concentrations in 10 patients aged 10–28 years with suspected infectious mononucleosis but with no serological evidence of this infection were not raised (mean ± SD = 1.5 ± 0.3 mg/l). Epstein-Barr virus in infectious mononucleosis, cytomegalovirus, and influenza A presented the strongest stimuli for increased $\beta_2$-microglobulin release, and in cytomegalovirus and influenza A this tended to persist during the convalescent period. In rubella there was a small increase in the mean serum $\beta_2$-microglobulin concentration. Infection with Mycoplasma pneumoniae produced a slight increase in the serum $\beta_2$-microglobulin concentration (mean ± SD = 2.1 ± 0.6 mg/l).

**C Reactive Protein**

The C reactive protein response was variable. Generally, there was no or only a small increase in C reactive protein concentration in the viral infections except in influenza and cytomegalovirus infection (Fig. 2). In influenza A infection the $\beta_2$-microglobulin and C reactive protein responses were significantly correlated ($r = 0.74$, $p = 0.001$; Spearman’s rank test), but the concentrations of these two plasma proteins were independent in the other virus infections and in the convalescent serum samples.

**Discussion**

These studies have shown that a raised serum $\beta_2$-microglobulin concentration can be induced by several forms of virus infection, but the mechanism of the response is largely conjectural. In infectious mononucleosis there is evidence that serum $\beta_2$-microglobulin concentrations are mainly a reflection of T cell activation. The sequence of lymphocyte response to infection with Epstein-Barr virus in infectious mononucleosis is unique, in that it affects a subset of B lymphocytes. The infection causes the B cells to proliferate, and this is followed by the appearance of activated suppressor T cells that inhibit further B cell activation. The T cells form the majority of the transformed “atypical” lymphocytes that are seen in the peripheral blood.

Cytomegalovirus produces a strong $\beta_2$-microglobulin response; the virus invades several tissues and does not have a specific lymphotrophic effect. In the infectious mononucleosis like syndrome due to cytomegalovirus infection the ratio of helper to suppressor cytotoxic T cells is decreased, which could be a reason for the high $\beta_2$-microglobulin concentrations, although it is not known whether the cytomegalovirus affects B lymphocytes. The serum $\beta_2$-microglobulin response in herpes simplex and varicella zoster virus was not pronounced in this series; the highest concentration, 7.6 mg/l, was found in a woman with herpes zoster one week after presentation. High concentrations of $\beta_2$-microglobulin in cerebrospinal fluid have been reported in herpes simplex meningitis; the combination of lymphocyte activation and brain cell necrosis may be the origin of the increased value. Influenza A virus is another strong stimulus for a $\beta_2$-microglobulin response. Destruction of polymorphonuclear leucocytes in the respiratory tract with release of leucocyte pyrogen and various kinins is a feature of the pathology, but the mechanism of the $\beta_2$-microglobulin response is unknown. The serum $\beta_2$-microglobulin concentrations, however, were considerably greater than those we have seen in 15 cases of bacterial pneumonias (mean ± SD = 3.1 ± 1.6 mg/l) (Juby, Brown, and Cooper; unpublished observations). Raised serum $\beta_2$-microglobulin concentrations have also been found in hepatitis B and non-A, non-B infections, but not in hepatitis A.

This indicates that the $\beta_2$-microglobulin response can occur in a variety of viral infections and is not restricted to the herpes virus group.

The C reactive protein responses in this series were generally similar to those noted in viral infections by Salonen and Vaheri. The lack of high concentrations among some of the groups, such as varicella zoster virus, may be due to the infections not being very severe or being complicated by secondary infection. In general, serum $\beta_2$-microglobulin concentrations are not influenced by the acute phase reaction to injury or bacterial infection. The reasons for the strong correlation between C reactive protein and $\beta_2$-microglobulin concentrations in influenza A infection are unclear; we did not find this correlation in the 15 bacterial pneumonias, where the median C reactive protein concentration was 60 mg/l and the range 5–227 mg/l. While lymphoid cells are the main source of increased serum $\beta_2$-microglobulin in disease, there is evidence that high concentrations can be associated with conditions that cause a pronounced stimulation of the macrophage and reticuloendothelial system, as in ineffective erythropoiesis and hypersplenism and in myelomonocytic leukaemia. Furthermore, leucocyte interferon will cause an increased expression of HLA antigens and $\beta_2$-microglobulin by lymphocytes in vitro. Whether this mechanism is important in the $\beta_2$-microglobulin response in vivo to any of the viruses we studied is still uncertain.

These studies have shown that an increase in serum $\beta_2$-microglobulin concentration may be induced by several types of viral infections. The
non-specific response of serum $\beta_2$-microglobulin and the variability of the response between patients means that the test has no diagnostic value. The main practical importance is in the interpretation of serum $\beta_2$-microglobulin concentrations in immunosuppressed patients—these include recipients of renal and bone marrow transplants, in whom infections with cytomegalovirus are common,23 and in children and younger adults with leukaemia or lymphoma, who are susceptible to viral and unusual infections. In immunosuppressive states, whether induced by drugs or part of the disease process, the lymphocyte subsets are altered, which may enhance the $\beta_2$-microglobulin response. In two patients sharp increases in serum $\beta_2$-microglobulin concentrations were noted, which coincided with cytomegalovirus infections shortly after bone marrow grafts at a time when the circulating lymphocyte count was low. In this context it is interesting that in the acquired immune deficiency syndrome a raised serum $\beta_2$-microglobulin concentration appears to be a feature in patients who have generalised lymphadenopathy as well as when the disease is complicated by Pneumocystis carinii infection or Kaposi’s sarcoma.24 25 The possible role of cytomegalovirus in the aetiology of Kaposi’s sarcoma in homosexual men suggests a connection between cytomegalovirus infection and raised serum $\beta_2$-microglobulin concentrations.10

References

6 Norfolk DR, Barnard DL, Child JA. Plasma $\beta_2$-microglobulin levels in bone marrow transplant patients with cytomegalovirus infection. Lancet 1984; i:685-6.

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