Chemokine response in children with SARS
P C Ng, C W K Lam, A M Li, C K Wong, T F Leung, F W T Cheng, K L E Hon, I H S Chan, E Wong, T F Fok

The chemokine response of eight children with serologically confirmed severe acute respiratory syndrome (SARS) was longitudinally monitored. All had raised plasma interferon $\gamma$ inducible protein (IP-10) concentrations, which suggested an active type 1 T-helper lymphocyte mediated immune response. High circulating IP-10 levels could facilitate viral clearance and might play a role in assisting the recovery of the patients.

Chemokines are secreted proteins that regulate the trafficking of specific populations of leukocytes to the site of injury and infection. Growing evidence suggests that these proinflammatory molecules represent an important component in the host defence by initiating specific immunological reactions. We have longitudinally monitored a panel of key chemokines, including interferon $\gamma$ inducible protein 10 (IP-10), monokine induced by interferon $\gamma$ (MIG), monocyte chemoattractant protein 1 (MCP-1), and regulated upon activation normal T cell expressed and secreted (RANTES) in a cohort of children with severe acute respiratory syndrome (SARS). The evaluation of inflammatory response to SARS coronavirus (SARS-CoV) is crucial for understanding the mechanisms of immune protection.

PATIENTS AND METHODS
The clinical, radiological, laboratory, and microbiological features of eight children with serologically confirmed SARS were described in detail in our previous report; the case numbers assigned to these children also corresponded with those in the same study.1 In brief, case 3 was the only patient who did not receive corticosteroid treatment. Cases 2 and 6 required pulse methylprednisolone, and case 6 also received intravenous ribavirin. All patients showed clinical improvement with subsidence of fever and complete or partial resolution of chest radiological changes, 2–7 days after improvement with subsidence of fever and complete or partial resolution of chest radiological changes.

Informed consent was obtained from the parents of all patients.

RESULTS
Four children (cases 4, 5, 6, and 8) did not have blood taken for chemokines on admission, and the youngest child (case 1) did not receive the final blood test. Table 1 summarises the chemokine results. Plasma IP-10 concentrations were substantially raised in all corticosteroid treated patients immediately before (range 3434–18 014 ng/l) and 1–2 days after corticosteroid treatment (range 1247–15 591 ng/l; see fig 1).

Plasma levels of MIG (range 149–988 ng/l) and MCP-1 (range 18–578 ng/l) were only mildly increased in the acute phase of illness. Five and two of the seven corticosteroid treated patients had abnormally increased plasma MIG and MCP-1, respectively. The overall trend suggested increased levels at the initial phase which were then followed by a decline in plasma concentrations with time. Plasma RANTES levels varied widely (range 4852–37 220 ng/l), but did not increase above the normal reference range in any of the patients.

Abbreviations: IP-10, interferon $\gamma$ inducible protein; MCP-1, monocyte chemoattractant protein 1; MIG, monokine induced by interferon $\gamma$; RANTES, regulated on activation normal T cell expressed and secreted; SARS, severe acute respiratory syndrome; SARS-CoV, SARS coronavirus; Th1, type 1 T helper

Figure 1. The change in plasma IP-10 concentrations at five different time points after the onset of illness—in eight children with SARS-CoV infection. All patients except case 3 received corticosteroids. The blood samples were obtained from case 3 for plasma chemokine measurements on days 3, 8, 10, 14, and 29 after the onset of fever.
The survival in infected animals. In contrast, treatment of site, thereby facilitating viral clearance; and (3) increasing following the natural recovery process of the disease. It is, was associated with corticosteroid treatment or simply whether the decline in chemokine levels with time.

DISCUSSION

As IP-10 and MIG are potent chemoattractants for activated type 1 T helper (Th1) lymphocytes, our findings suggest that SARS-CoV activates mainly the Th1 immune response. Early and prominent expression of SARS-CoV activates mainly the Th1 immune response.

As IP-10 and MIG are potent chemoattractants for activated T cells, they play an important role in the development of Th1 immune response to SARS-CoV infection.

There are limitations in this study. Firstly, the plasma chemokine levels were only monitored in a small number of paediatric patients; however, their disease pattern was a good reflection of paediatric SARS, as the great majority (96%) of affected children did not require intensive care treatment in Hong Kong. Further, this pattern of chemokine response is similar to that observed in adult SARS patients. Secondly, in the absence of a matched control group, it is difficult to be certain whether the decline in chemokine levels with time was associated with corticosteroid treatment or simply following the natural recovery process of the disease. It is, however, worth noting that circulating chemokines in case 3 (the only patient who did not receive corticosteroids) also followed a similar decreasing trend (fig 1).

In summary, the substantial increase in plasma IP-10 suggests an active Th1 mediated antiviral response to SARS-CoV. High circulating IP-10 can facilitate viral clearance and may play a role in assisting the recovery of the patients.

There is a lack of a significant upsurge in circulating RANTES level is unexpected, but correlates with our clinical observation that the majority of patients do not have clinical manifestations or spirometry features suggestive of postviral obstructive airway disease.

Table 1 Changes in chemokine profile of children with SARS (excluding case 3) before and after corticosteroid treatment

<table>
<thead>
<tr>
<th>Plasma chemokine concentrations (ng/l)</th>
<th>Immediately before corticosteroid treatment (n = 7)</th>
<th>1–2 days after corticosteroid treatment (n = 7)</th>
<th>7–10 days after corticosteroid treatment (n = 7)</th>
<th>3–6 weeks after corticosteroid treatment (n = 6)</th>
<th>Normal reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIG</td>
<td>421 (397–878)</td>
<td>509 (405–878)</td>
<td>486 (174–575)</td>
<td>200 (170–293)*</td>
<td>37–463</td>
</tr>
<tr>
<td>MCP-1</td>
<td>108 (84–182)</td>
<td>93 (47–134)</td>
<td>47 (33–66)*</td>
<td>53 (23–78)*</td>
<td>18–152</td>
</tr>
<tr>
<td>RANTES</td>
<td>26979 (21160–29192)</td>
<td>25613 (11661–35233)</td>
<td>33669 (22252–36711)</td>
<td>22974 (16686–35020)</td>
<td>10349–46704</td>
</tr>
</tbody>
</table>

Results are median (interquartile range).

*p<0.05 (comparison of plasma chemokine concentrations before and after corticosteroid treatment).

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