INTRODUCTION

Cytomegalovirus (CMV), first described in 1956, is a double-stranded DNA virus belonging to the herpes virus family. Cytomegalovirus infection is prevalent worldwide, although symptomatic CMV illness is usually confined to immunocompromised individuals. Earlier reports from the Christian Medical College, Vellore, showed that in southern India, more than 70% of children had complement-fixing antibodies to CMV by the age of 4 years and there was a higher prevalence of antibody (98%) in cord blood samples. A survey using a sensitive ELISA test demonstrated immunoglobulin G antibodies in 92% of older children and adults. These prevalence rates are much higher than reports from temperate zone, industrialized countries. The presence of characteristic inclusion bodies in haematoxylin and eosin (HE)-stained histological samples is regarded as being sensitive and specific for CMV infection, especially for samples from the gastrointestinal tract. Evidence of CMV infection of the gastrointestinal mucosa, as shown by the presence of intranuclear or intracytoplasmic inclusions, were found in 54 of 6323 patients who had mucosal biopsies during the period January 1989 to December 1996 (0.85%) at the Christian Medical College and Hospital, Vellore. A detailed analysis of this material is reported.

METHODS

A total of 6580 mucosal biopsies were available from different parts of the gastrointestinal tract from diag-
nostic investigations carried out in the Department of Gastrointestinal Sciences on 6323 patients in the 8-year period from January 1989 to December 1996. These included endoscopic biopsies from the rectum, colon, ileum, duodenum, stomach and oesophagus and suction mucosal biopsies of the jejunum (Table 1). All biopsies were fixed in Bouin’s or buffered neutral formalin and paraffin sections were stained with HE. Sections were examined by two pathologists independently and CMV inclusions were noted. Typical CMV inclusions (Fig. 1) have ‘owl’s eye’ nuclear inclusions (Cowdry bodies) and eosinophilic inclusions in the cytoplasm of enlarged cells.\(^{10,11}\) In addition, three types of atypical inclusions (Fig. 2) as described by Schwartz and Wilcox\(^{12}\) were also found. The cell types (epithelial, stromal, endothelial, macrophage) in which the inclusions were found were noted (Table 2). The endoscopic appearance and, particularly, the presence of ulcers was also analysed.

**RESULTS**

The 54 patients, from whom the 61 biopsies with evidence of CMV inclusions were obtained, ranged in age from 5 to 71 years (mean 38, median 45 years). There

<table>
<thead>
<tr>
<th>Site of biopsies</th>
<th>Total biopsy</th>
<th>Immuno-compromised ((n=37))</th>
<th>Immuno-competent ((n=17))</th>
<th>Total</th>
<th>Prevalence per 1000 biopsies</th>
<th>Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus</td>
<td>616</td>
<td>21</td>
<td>21</td>
<td>34.1</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>704</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>7.1</td>
<td>2</td>
</tr>
<tr>
<td>Duodenum</td>
<td>334</td>
<td>1</td>
<td>1</td>
<td>3.0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>207</td>
<td>2</td>
<td>2</td>
<td>9.7</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>4719</td>
<td>16</td>
<td>16</td>
<td>32</td>
<td>6.8</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6580</strong></td>
<td><strong>44</strong></td>
<td><strong>17</strong></td>
<td><strong>61</strong></td>
<td><strong>9.3</strong></td>
<td><strong>32</strong></td>
</tr>
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*Figure 1* Photomicrograph showing a typical or Cowdry-A inclusion: an enlarged cell with an intranuclear eosinophilic inclusion surrounded by a clear halo with chromatin margination (arrow), HE.

*Figure 2* Photomicrograph showing (a) a type I atypical cytomegalovirus (CMV) inclusion body (arrow) in an enlarged endothelial cell with an eccentric nucleus, an ill-defined nuclear margin surrounded by an amphophilic zone and with occasional minute intracytoplasmic granules. (b) Type II atypical CMV inclusion body (arrow) in an enlarged smooth muscle cell with a elongated dense eosinophilic smudged nucleus, moderate to scant cytoplasm and absence of a well-formed inclusion body. (c) Type III atypical CMV inclusion body (arrow) is only seen in the glandular epithelium with cytomegaly and enlarged nucleus, with an occasional crystalline texture but lacking the well-formed inclusion and halo, HE.
were more males (40:14), but this reflects the sex distribution of patients who underwent endoscopic biopsies. The 37 patients who were immunocompromised included six with acquired immune deficiency syndrome, four post-bone marrow transplants, seven post-renal transplants, 12 with ulcerative colitis on steroid therapy and eight patients with malignant neoplasms on chemotherapy. The other 17 patients were apparently immunocompetent, but all of them were severely ill.

The most frequent site of detection of CMV inclusions was the oesophagus (Table 1) with a prevalence of 34 per thousand. All these patients were immunocompromised individuals. The jejunal mucosa had the next highest frequency (9.7 per thousand), followed by the stomach and the large intestine and rectum (Table 1). In 16 of the 17 immunocompetent patients, the large intestine or rectum was the site of the lesion.

Ulcerated lesions were detected endoscopically in 32 of the 54 patients (Table 1). Ulcerated lesions were found in 70% (26) of the 37 immunocompromised individuals, but in only 35% (6) of the 17 patients with normal immune status. This difference was not statistically significant. Stromal cells (41 patients) and endothelial cells (30 patients) were the most commonly infected cell type. Epithelial cell and macrophage involvement were relatively infrequent (Table 2) and there was no evidence of epithelial cell infection at or near ulcer margins. Significantly more involvement of stromal cells was found in the ulcerated group (P<0.02), while there was no such difference in endothelial cell involvement.

Twelve patients had typical inclusion bodies only while 17 had atypical inclusions only. In 25 patients both typical and atypical inclusions were present. Atypical inclusions were only found in macrophages. Atypical inclusions were more common in the immunocompromised (90%) than in the immunocompetent (47%).

**DISCUSSION**

The detection of CMV inclusions in 9 per thousand endoscopic biopsies of the gastrointestinal mucosa is a reflection of the high prevalence of CMV infection in this population. While this high prevalence can be attributed to the prevalence of ulcerated CMV lesions in the small number of immunocompromised subjects who were investigated, the detection of CMV inclusion bodies in 17 immunocompetent but severely ill individuals raises the possibility of reactivation of a latent infection in a population with a high prevalence of CMV infection.

Oesophageal lesions were found only in immunocompromised individuals. Two reports from the temperate zones reported a less than 10% prevalence of CMV in oesophageal biopsies although another reports a higher prevalence. The high prevalence of oesophageal CMV infection in the present study raises the possibility that this may be the result of ingestion of the virus from the environment in an area with a high prevalence of the infection. It may also be that the oesophageal mucosa is a common site for latent infection that is activated when the immune response is compromised.

The characteristic inclusions make the histopathological diagnosis straightforward. Several reports suggested that the use of immunohistochemical or DNA hybridization techniques may only marginally enhance the diagnostic yield and are not more specific or sensitive techniques. The presence of CMV inclusion bodies indicates active viral replication leading to pathological lesions. Atypical inclusions were seen more frequently in immunocompromised individuals suggesting that the typical inclusions are the end result of viral infection and tissue response in an immunocompetent host, the nature of which is as yet poorly understood. The most commonly affected cell types were stromal cells and endothelial cells. It has been suggested that vascular occlusion from the infection of endothelial cells may play a role in the pathogenesis of ulceration, which is frequently associated with CMV infection. The results reported here do not support this hypothesis as a significantly higher prevalence of CMV in patients with ulcerated lesions was found only in stromal cells.

This retrospective survey of gastrointestinal mucosal biopsies from a population with a high prevalence of CMV infection suggests that it is important to keep this diagnosis in mind and search for CMV inclusion bodies, especially when mucosal biopsies from ulcerated lesions are being evaluated and to be aware of the significance of atypical inclusions, especially in immunocompromised patients.

**ACKNOWLEDGEMENTS**

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REFERENCES