Hypogammaglobulinaemia secondary to reflux oesophagitis

V Spoulou, C Melville, M Young, P Milla, C Newman, G Morgan

Abstract
A 7 year old girl referred for investigation of hypogammaglobulinaemia had hypoalbuminaemia and severe necrotising oesophagitis on oesophagogastroduodenoscopy. Nissen fundoplication resolved all clinical and laboratory abnormalities, but she remains under surveillance because of histological findings of Barrett’s oesophagitis. Erosive reflux oesophagitis can present with minimal localising symptoms, and hypogammaglobulinaemia and hypoalbuminaemia, presumably from protein loss.
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Keywords: hypogammaglobulinaemia, hypoalbuminaemia, reflux oesophagitis, fundoplication.

Oesophagitis is a common complication of gastro-oesophageal reflux. Although retrosternal pain and iron deficiency anaemia are well recognised, the association of reflux oesophagitis with hypoalbuminaemia is reported infrequently.1 There are no reports of hypogammaglobulinaemia. We present a 7 year old girl with severe histologically proved oesophagitis and severe oesophageal reflux on pH monitoring, whose hypoalbuminaemia, hypogammaglobulinaemia, and oesophagitis resolved rapidly and completely after antireflux surgery.

Case report
A 7 year old girl was admitted for investigation of hypogammaglobulinaemia. Symptoms had started 14 months earlier, after a febrile illness associated with mild cough and vomiting. She had general malaise, poor weight gain, and vague abdominal pain. Investigations performed at the local hospital five months later showed a haemoglobin concentration of 127 g/l and serum albumin of 39 g/l, which over the succeeding nine months fell to 89 g/l, and 21 g/l respectively. Her platelet count was raised. A small bowel meal was normal, and, in particular, there was no evidence of terminal ileitis. She had experienced no significant previous infections and had received standard immunisations. Her parents were healthy and there was no significant family history. Her height and weight were just below the third centile and apart from mild diffuse abdominal tenderness, physical examination was normal.

Investigations confirmed her anaemia with a haemoglobin concentration of 89 g/l, and hypoalbuminaemia with serum albumin of 20 g/l. Dietary assessment showed a marginally low protein intake of 30 g/day. Liver function tests were normal, as was the stool α1-antitrypsin concentration at 0.4 mg/g stool (normal range 0.05 to 0.48). Colonoscopy and biopsy specimens taken from jejunum and terminal ileum, were also normal. Tests for immunodeficiency showed normal lymphocyte numbers of 4.36 x 10^9/L, with normal distribution of lymphocyte subpopulations using a range of monoclonal antibodies, normal proliferative response to phytohaemagglutinin, and hypogammaglobulinaemia with low concentrations of all IgG subclasses but normal IgM and IgA (table). However, there were protective antibody levels to diphtheria and tetanus. An autoantibody screen was negative including antinuclear antibodies and antibodies to gastric parietal cells, smooth muscle, mitochon-
dridia, reticulin, and gliad.

An oesophagogastroduodenoscopy was performed because of persisting concerns about a gastrointestinal abnormality. Macroscopically there was severe necrotising oesophagitis with slough and inflammatory pseudopolyps, extending from the lower oesophageal sphincter to mid-oesophagus. Histologically the appearances were suggestive of herpetic oesophagitis (figure A), although no intranuclear or intracytoplasmic inclusions were present, and immunostaining for herpes simplex I and II and viral culture of biopsy specimens were negative. She was treated with cimetidine 10 mg/kg three times a day, domperidone 0.2 mg/kg three times a day, and despite lack of specific confirmation of herpetic infection, acyclovir 1-4 g/m^2/day, the latter for eight weeks, because of the possibility of an underlying primary immunodeficiency. Three months later she remained symptomatically unchanged, anaemic, hypoalbuminaemic, and hypogammaglobulinaemic, but stool α1-antitrypsin was now marginally raised. The diagnosis was now thought to be either primary immunodeficiency with secondary herpetic oesophagitis, or gastrointestinal protein loss possibly from reflux oesophagitis. To help distinguish between these possibilities a trial of intravenous immunoglobulin treatment was started at 0.4 g/kg every three weeks, and antireflux medication continued. After three months her symptoms were unabated, with

Changes in serum albumin, immunoglobulins, haemoglobin and α1-antitrypsin, with alterations during treatment

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Before IVIG</th>
<th>After IVIG</th>
<th>After IVIG (ND)</th>
<th>Fundoplication</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (g/l)</td>
<td>3.7–18.8</td>
<td>2.10</td>
<td>2.25</td>
<td>4.87</td>
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<tr>
<td>IgA (g/l)</td>
<td>0.3–1.3</td>
<td>0.34</td>
<td>0.32</td>
<td>0.47</td>
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<tr>
<td>IgM (g/l)</td>
<td>0.5–2.2</td>
<td>0.61</td>
<td>0.78</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>35–55</td>
<td>24</td>
<td>21</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>115–155</td>
<td>89</td>
<td>118*</td>
<td>125</td>
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<tr>
<td>Stool α1-antitrypsin (mg/g)</td>
<td>0.05–0.48</td>
<td>0.4</td>
<td>0.6*</td>
<td>ND</td>
<td></td>
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</tbody>
</table>

*Patient on iron supplements. IVIG=intravenous immunoglobulin; ND=not done.
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Investigation of hypogammaglobulinaemia

A

(A) Oesophageal biopsy specimen showing heavily
inflamed squamous mucosa, with incipient ulceration
and an intraepithelial bulla. The appearances, although
non-specific, are suggestive of herpes simplex oesophagitis
(magnification ×500). (B) Oesophageal biopsy specimen,
taken above the cardio-oesophageal junction, showing
metaplastic gastric body type mucosal glands, including
parietal cells (arrows). The appearances are typical of
Barrett’s oesophagus (magnification ×120).

Discussion

Investigation of hypogammaglobulinaemia, especially, if associated with hypo-
albuminaemia, requires exclusion of protein

loss. It may be necessary to investigate the
whole length of gastrointestinal tract to identify
the source. Increased losses of serum proteins
such as albumin, immunoglobulins and transferrin, can occur as a result of lymphatic
blockage, mucosal damage by inflammatory
bowel disease, or intestinal lymphangiectasia. However, hypogammaglobulinaemia has not

been described in association with reflux oesophagitis.

The association of hypoalbuminaemia and reflux oesophagitis was first described by Herbst
et al. Fung et al reported that 27/121 patients

requiring Nissen fundoplication for the correc-
tion of their gastro-oesophageal reflux had low

serum albumin concentrations. They found significant correlation between presence of
hypoalbuminaemia, features of Barrett’s

oesophagus, and the severity of reflux. Although it seems likely that protein loss is
due to defective barrier function at the site of
intestinal inflammation, the rate of consequent
protein loss may be too low or too intermittent
to be demonstrated by chromium labelled
albumin scanning. Intermittent protein loss may also explain the initially normal stool

α1-antitrypsin concentration in our patient,

normally a sensitive indicator of stool protein loss. Dietary protein intake, which was
marginally low, was not sufficient to explain her hypoalbuminaemia in the presence of

normal liver function.

The severity of the oesophagitis was compatible with herpes infection associated with an
underlying primary immunodeficiency. Histologically, reflux oesophagitis usually results in
superficial erosions, often with an eosinophilic or chronic inflammatory infiltrate. Severe
erosions are suggestive of herpetic oesophagitis, and are usually associated with severe oral
lesions, systemic upset, and an identifiable immunodeficiency. Streptococcal efforts using
viral titres, cultures, and immunostaining tech-
niques of biopsy specimens should be made in an attempt to confirm the diagnosis, particularly if a
primary immunodeficiency is suspected.

In this case the presumptive diagnosis was re-examined in view of lack of confirmation of
herpetic infection by specific immunostaining

or cultures, failure to respond to acyclovir, and

no increase of serum immunoglobulins when on

appropriate replacement treatment. A pH

study confirmed persistent severe oesophageal
reflux that failed to respond to maximal medical
treatment and led to appropriate surgery with
resolution of all clinical and laboratory abnor-
malities. The original choice of a barium meal

and follow through, rather than a small bowel

meal, in the search for inflammatory bowel
disease, would probably have led to an earlier
diagnosis of the gastro-oesophageal reflux.

Reflux oesophagitis sufficient to cause
hypogammaglobulinaemia, hypoalbuminaemia, and failure to thrive, can occur with minimal
localising symptoms.

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children requiring Nissen fundoplication for the manage-


237-46.

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4 Herbst J, Johnson G, Oliveros M. Gastroesophageal reflux with protein-losing enteropathy and finger clubbing.


5 Thomas DW, Sinatra FR, Merritt RJ. Random fecal alpha-1

antitrypsin concentration in children with gastrointestinal

6 Dahms BB, Rothestein FC. Mucosal biopsy of the oesopha-