Hypogammaglobulinaemia secondary to reflux oesophagitis

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Abstract

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

(Arch Dis Child 1995; 72: 245-246)

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 α_1 -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 $4.36 \times 10^9/l$, 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, mitochondria, reticulin, and gliadin.

An oesophagogastrroduodenoscopy 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),² 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/m²/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 α_1 -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

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Accepted 14 November 1994

Changes in serum albumin, immunoglobulins, haemoglobin and α_1 -antitrypsin, with alterations during treatment

	Normal range	Before IVIG	After IVIG	After Nissen fundoplication
IgG (g/l)	3.7-18.8	2.10	2.25	4.87
IgA (g/l)	0.3-1.3	0.34	0.32	0.47
IgM (g/l)	0.5-2.2	0.61	0.78	1.55
Albumin (g/l)	35-55	24	21	37
Haemoglobin (g/l)	115-155	89	118*	125
Stool α_1 -antitrypsin (mg/g)	0.05-0.48	0.4	0.6	ND

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

(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 $\times 500$). (B) Oesophageal biopsy specimen, taken above the cardio-oesophageal junction, showing metaplastic gastric body type mucosal glands, including parietal cells (arrow). The appearances are typical of Barrett's oesophagus (magnification $\times 120$).

continuing hypoalbuminaemia and no significant increase of IgG concentrations despite adequate replacement treatment. This was highly suggestive of protein loss. A 24 hour pH study revealed severe gastro-oesophageal reflux (19% acid reflux, with infrequent prolonged episodes lasting up to an hour).

After a repeated endoscopy that confirmed persistence of severe oesophageal inflammation, a Nissen fundoplication was performed. Histology of samples taken during the operation showed metaplastic gastric body type mucosa, typical of Barrett's oesophagus (figure B).

Convalescence was uncomplicated, with rapid recovery from symptoms and correction of all laboratory parameters. Biopsy specimens taken six and 18 months after the fundoplication, however, showed persistent features of Barrett's oesophagus and she remains under surveillance for malignant changes of the metaplastic epithelium.

Discussion

Investigation of hypogammaglobulinaemia, especially if associated with hypoalbuminaemia, 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.³ 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.*⁴ Fung *et al.* reported that 27/121 patients requiring Nissen fundoplication for the correction of their gastro-oesophageal reflux had low serum albumin concentrations.¹ 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.⁴ Intermittent protein loss may also explain the initially normal stool α_1 -antitrypsin concentration in our patient, normally a sensitive indicator of stool protein loss.⁵ 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.⁶ Severe erosions are suggestive of herpetic oesophagitis, and are usually associated with severe oral lesions, systemic upset, and an identifiable immunodeficiency.² Strenuous efforts using viral titres, cultures, and immunostaining techniques 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 abnormalities. 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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