Pitfalls in diagnosing coeliac disease

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Abstract

***Aims*—To highlight the pitfalls in the diagnosis of coeliac disease and to make recommendations for its diagnosis and the management of refractory cases with equivocal histology.**

***Methods*—Six patients, referred since 1989 with a diagnosis of coeliac disease based on duodenal biopsy specimens taken at endoscopy, and who failed to respond to a gluten-free diet were studied. All patients were subjected to peroral jejunal biopsy. Morphometric analysis of villus height:crypt depth ratios, surface enterocyte cell heights, and intraepithelial counts was used to aid in the assessment of equivocal histology.**

***Results*—Subsequent small intestinal biopsy specimens both taken when the patients were following a gluten-free diet and after gluten challenge were normal in all cases. Morphometric analysis and intraepithelial counts were normal.**

***Conclusions*—Misinterpretation of the original slides was often due to poor sample quality and tangential sectioning. Failure to respond to a gluten-free diet should always raise doubt regarding the initial diagnosis, especially when the findings are normal. For correct diagnosis at least three distal duodenal biopsy specimens should be taken simultaneously, and these should be of an adequate size and correctly orientated. Review by a histopathologist experienced in gastrointestinal diagnosis is essential in difficult cases. Quantitative morphometric analysis is helpful in equivocal cases, and jejunal suction biopsy, following a gluten challenge, may be necessary in patients refractory to treatment.**

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The gold standard of diagnosis in coeliac disease remains the histological analysis of small intestinal mucosal biopsy specimens. Since the introduction of upper gastrointestinal endoscopy in the early 1970s, endoscopic forceps biopsy of the first and second parts of the duodenum has replaced peroral suction biopsy as the mainstay of diagnosis.[1] The ready accessibility of the duodenum to the endoscopist and the routine sampling of duodenal mucosa for the investigation of patients with anaemia and diarrhoea has meant that the pathological diagnosis of duodenal samples has become increasingly more common. Anecdotal reports from gastroenterologists suggesting misdiagnosis of coeliac disease are relatively common. We reviewed our recent experience, as a tertiary referral centre for patients with coeliac disease, to highlight common pitfalls in diagnosis and make recommendations for the diagnosis and management of difficult cases.

Methods

Six women with a mean age of 26·3 years (range 19–32) with a diagnosis of coeliac disease had been referred since 1989 for a tertiary opinion. All the patients had failed to respond to a gluten-free diet for a mean duration of 23 months (range 7–36). Their initial diagnosis was made on the basis of endoscopic duodenal forceps biopsy specimens which had been reported as showing subtotal villous atrophy. Subsequent small intestinal biopsy specimens when the patients were following a gluten-free diet were normal.

We routinely investigate patients who fail to respond clinically to a gluten-free diet by subjecting them to suction peroral jejunal biopsy following a gluten challenge. In all cases the histology after the challenge was normal. We also routinely request the initial histology to review it in conjunction with a pathologist experienced in gastrointestinal histopathology.

Results

Morphometric analysis of villus height:crypt depth ratios (VH:CD, mean (SD) 4·1 (1·5), surface enterocyte cell heights (SECH, 34·4 (12·6)) μm, and intraepithelial counts (IEL, 18·5/100 (6·8)) epithelial cells was used to assist with the diagnosis. The results were normal in all the biopsy specimens. VH:CD ratios are not measured in villi sectioned tangentially. The SECH is measured in the middle third of the villus from the villus-crypt junction. IEL are darkly-staining nuclei which are counted on haematoxylin and eosin or immunohistochemical sections and expressed as IEL/100 epithelial cells. Results are expressed as means (SD) of multiple measurements.

Laboratory investigations of the patients were within normal limits with the exception of the patient with Crohn's disease who had an iron-deficient anaemia. One patient had raised anti-gliadin antibodies; none had detectable anti-reticulin or anti-endomysial

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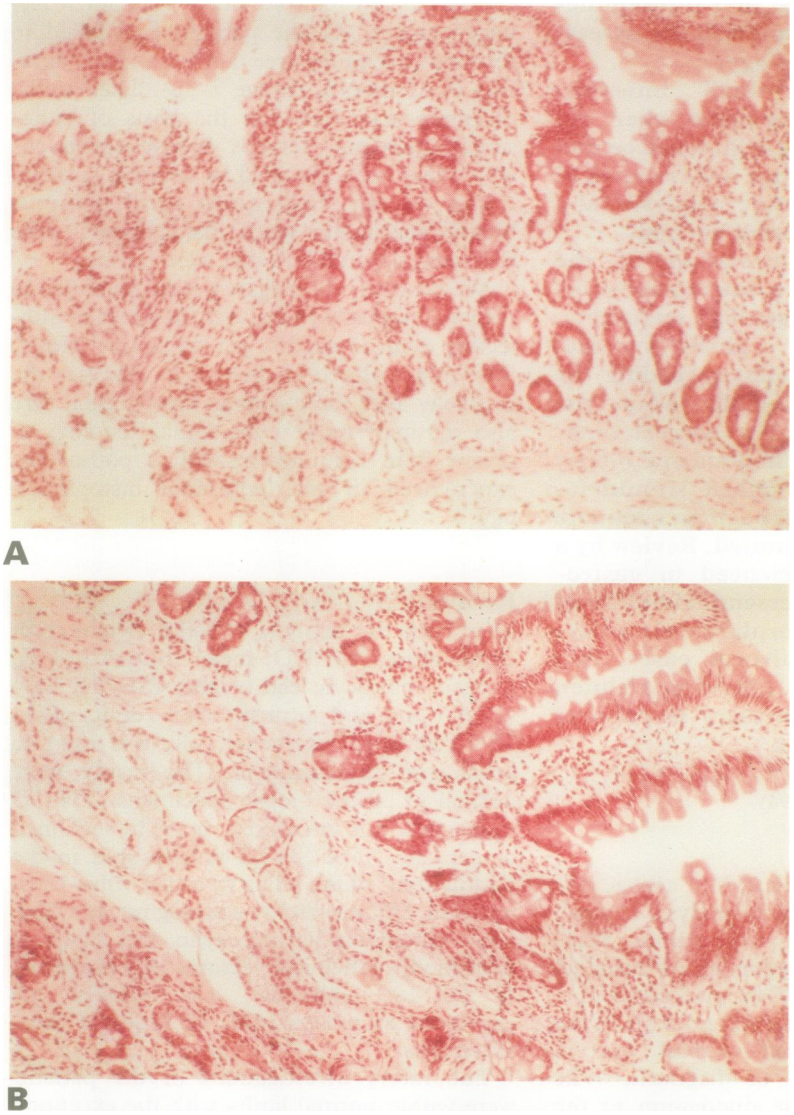
Cases referred with a diagnosis of coeliac disease since 1989

			Initial biopsy					
Case No	*Age*	*Sex*	*GFD**	*VH:CD†*	*SECH‡*	*IEL***	*Diagnosis*	*t (y)¶*
1	25	F	1·5	4·3	26·8	16·6	Irritable bowel syndrome	8·0
2	28	F	3·0	3·1	28·4	20·6	IBD††	3·0
3	23	F	1·3	4·3	37·4	19·0	Irritable bowel syndrome	4·0
4	32	F	2·2	4·1	31·9	20·8	Migraine	2·5
5	31	F	3·0	3·5	41·8	21·6	Irritable bowel syndrome	3·0
6	19	F	0·6	5·3	40·2	12·6	Crohn's disease	2·0

*Duration of gluten-free diet (years) before referral.
†Villus height:crypt depth ratio (normal range: 3–5).
‡Surface enterocyte cell height (normal range: 29–34 μm).
**Intraepithelial lymphocyte count/100 epithelial cells (normal range: 10–30).
δInterval between clinical presentation and diagnosis (years).
††Post-infectious inflammatory bowel disease.

antibodies. All patients have tolerated a normal diet, and have been followed up for seven months to three years.

The clinical features, results of morphometric analysis of the initial biopsy specimens, and eventual diagnoses, with the time interval between initial presentation and final diagnosis, are summarised in the table.



Poor sectioning can give a false impression of subtotal villous atrophy. Two sections taken from the same patient: One (A) was interpreted by the referring hospital as showing subtotal villous atrophy; (B) was taken from the same slide, showing normal features (haematoxylin and eosin).

Discussion

Overdiagnosis of villous atrophy may occur because of misinterpretation of suboptimally prepared sections, the samples being too small, in poor condition, or being cut tangentially. It has even been known for gastric pyloric mucosa to be submitted labelled as "duodenal biopsy". Forceps biopsy samples are smaller in size than those obtained by suction. Proper orientation of the specimen on filter paper, with the villi uppermost, helps to ensure that the sections are cut correctly. The normal VH:CD ratio is invalid when the villi overlie Brunner's glands. Brunner's glands are found predominantly in the proximal duodenum, and thus distal biopsy specimens are preferred. Measurement of the VH:CD, IEL, and SECH, commonly used for research purposes, is useful in equivocal samples.

Failure to respond to a gluten-free diet should raise the possibility of either poor dietary compliance or an incorrect diagnosis. The criteria for the diagnosis of coeliac disease stipulate the histological finding of a characteristic small intestinal mucosal abnormality, followed by a reasonably rapid clinical remission on a gluten-free diet.[2 3] Further biopsy specimens are indicated if the patients are initially asymptomatic (first order relatives of probands) or if the clinical response to a gluten-free diet is equivocal. A gluten challenge (40 g of gluten or four slices of normal bread per day for at least two weeks for adults and six weeks for children) formed part of the original criteria, but is now reserved for cases where there is doubt concerning the initial diagnosis. The duration of the challenge may be reduced if the patients become clinically symptomatic.

For the correct diagnosis of coeliac disease, we therefore conclude that:

(i) a minimum of three biopsy specimens distal to the first part of the duodenum should be taken at the time of the initial endoscopy;

(ii) the biopsy specimens should be correctly orientated, be of adequate size, and be reviewed by an experienced histopathologist.

Where histological diagnosis is difficult, we recommend that:

(iii) VH:CD, IEL, and SECH should be measured, and

(iv) suction biopsy of the proximal jejunum is performed, following an adequate gluten challenge, if necessary.

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2 Meeuwisse G. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970;59:461–3.
3 Walker-Smith J, Guandalini S, Schmitz J, Shmerling D, Visakorpi J. Revised criteria for diagnosis of coeliac disease. *Arch Dis Child* 1990;65:909–11.