The association between webs, iron and post-cricoid carcinoma

MORAG CHISHOLM
M.D.

Royal South Hants Hospital, Southampton

Summary

The association of iron deficiency anaemia, post-cricoid webs and carcinoma is controversial. The main findings in a recent study which re-examined this problem are presented here. It was shown that the majority of patients with a post-cricoid web have evidence of iron deficiency but that only about 10% of patients with iron deficiency develop post-cricoid webs. Factors which might be important in the pathogenesis of a post-cricoid web have been looked for and a few significant points noted. The main findings were an increased frequency of angular stomatitis and edentia, thyroid disease and thyroid cytoplasmic antibodies in patients with webs compared with patients with iron deficiency anaemia without a web.

Follow-up studies in patients with a post-cricoid web or Paterson-Kelly syndrome show an increased frequency of post-cricoid carcinoma ranging from 4 to 16% in different series and the association is even more striking in patients presenting with post-cricoid carcinoma. It is concluded that the available evidence confirms the association between iron deficiency, post-cricoid webs and carcinoma but the mechanism of the production of these changes is not yet understood.

THE syndrome of post-cricoid dysphagia, glossitis, koilonychia and iron deficiency anaemia is variously known as the Paterson-Kelly or Plummer-Vinson syndrome and sideropaenic dysphagia. Since the early descriptions there has been disagreement as to whether the iron deficiency was important in the aetiology of the web or whether it was a secondary manifestation consequent upon the dysphagia. Evidence of iron deficiency is not always found in patients in whom a post-cricoid web has been diagnosed; indeed in an epidemiological study in Wales, Elwood and associates (1964) concluded that 'there is no evidence of the existence in the general population of a syndrome in which dysphagia is associated with anaemia'. Similarly the association between post-cricoid carcinoma and pre-existing sideropaenic dysphagia has been debated and the frequency with which it occurs has varied in different series.

My colleagues and I in the Nuffield Department of Medicine at Oxford have approached the problem in two ways. Firstly by a follow-up study of patients

with post-cricoid webs seen at the Radcliffe Infirmary over a 15 year period from 1949 until 1964 (Chisholm *et al.*, 1971a), and secondly by a prospective study in which patients with various conditions reported to be associated with post-cricoid webs and healthy control subjects have been examined for evidence of a web by means of cinefluorography of swallowing (Chisholm *et al.*, 1971b).

The radiological features of a post-cricoid web were first described by Waldenström and Kjellberg (1939). The radiological features we used to diagnose a post-cricoid web are shown in Table 1; two or more webs were present in one-third of our cases. Some of these features are well illustrated in Fig. 1,

TABLE 1. Radiological features of a post-cricoid web

1. In lower lateral food channels or oesophagus commonly at level of cricopharyngeal sphincter.
2. Anterior or anterolateral; may encircle lumen.
3. Length of projection more than thickness (1-2 mm).

FIG. 1. Radiograph showing multiple post-cricoid webs.

which shows two well-developed webs in a patient with long-standing dysphagia where almost half the lumen of the oesophagus is obstructed. As can be seen from Table 2 we have found cinefluorography of swallowing to be superior to a conventional barium swallow in the diagnosis of a web. In thirty-one patients in whom both investigations were carried out a web was seen in a significantly greater proportion of patients by means of cinefluorography. In six of the seventy-two patients seen in the follow-up study, the diagnosis was made on oesophagoscopy alone, but it has also been our experience that well-defined webs seen radiologically may subsequently be missed at oesophagoscopy.

TABLE 2. Diagnosis of post-cricoid web

Investigation	Results		
	No. of patients	Web seen	No web seen
Barium swallow	20	12	8
Cinefluorography	15	15	nil
Both investigations			
Barium swallow		17	14
Cinefluorography	31	28	3
Oesophagoscopy only	6		
Total	72		

Biopsy of the web may be difficult but was obtained in ten of the forty-five patients in whom oesophagoscopy was carried out. In only half of these was a histological abnormality noted. The

abnormal features seen in one such biopsy are shown in the next two figures. Figure 2 is a general view showing thickening of the epithelial layer with irregular acanthosis and subepithelial inflammation. Figure 3 is a high power view of the basal layers showing chronic inflammatory infiltrate.

Certain clinical features of our patients with post-cricoid webs are of interest in relation to their pathogenesis. The age distribution of our seventy-two patients seen in the follow-up study is shown in Fig. 4. This followed the same pattern of age distribution of a group of patients with iron deficiency anaemia without a web; webs were uncommon in patients under 30, and three-quarters of our patients were aged 40 years or over. The striking female preponderance noted in several reported series (Jones, 1961; Jacobs and Kilpatrick, 1964) was confirmed in our own where sixty-six of the seventy-two patients (92%) were women, and is consistent with the greater frequency of severe chronic iron deficiency anaemia in women. However, when a group of men and women with iron deficiency anaemia were examined prospectively by means of cinefluorography of swallowing, a post-cricoid web was seen in approximately equal proportions of both sexes (Chisholm *et al.*, 1971b).

The association between a post-cricoid web and iron deficiency in the patients in our follow-up study is summarized in Table 3. More than half had iron deficiency anaemia at diagnosis, a further 10% were iron deficient on investigation and a past history of iron deficiency anaemia was noted in 21%. Thus in 88% a definite link between iron deficiency and a

FIG. 2. Histological appearance of post-cricoid web.

FIG. 3. High power view of section shown in Fig. 2.

FIG. 4. Age distribution of seventy-two patients with a post-cricoid web.

post-cricoid web was established. Further evidence favouring an association between iron deficiency and post-cricoid dysphagia is the improvement in the dysphagia which occurs on treatment with iron, and this was observed in the majority of our patients.

TABLE 3. Association between iron deficiency anaemia and post-cricoid web (seventy-two patients)

1. Iron deficiency anaemia at diagnosis	57%
2. Sideropaenia at diagnosis	10%
3. Past history of iron deficiency	21%
4. No definite evidence	12%

Of interest are the associated conditions observed in the seventy-two patients with post-cricoid webs (Table 4). The striking features are the high incidence of thyroid disease and malignant disease, associations which have previously been noted. Of the

eleven patients with malignant disease, six had a carcinoma in the upper gastrointestinal tract, details of which are given later.

TABLE 4. Associated conditions in seventy-two patients with a post-cricoid web

	No. of patients	
Thyroid disease	11	(15%)
Malignant disease	11	(15%)
Peptic ulcer	9	(12.5%)
Rheumatoid arthritis	8	(11%)
Pernicious anaemia	5	(7%)
Hiatus hernia	5	(7%)

In our prospective study (Table 5) patients with iron deficiency anaemia, healthy controls and patients with a variety of disorders previously shown to co-exist with a post-cricoid web were examined by

means of cinefluorography of swallowing for the presence of a web. In all but five of the thirty-two patients with a web, irrespective of the index diagnosis, there was evidence of iron deficiency, confirming the association between these two conditions noted in the follow-up study.

TABLE 5. Post-cricoid webs in iron deficiency anaemia and miscellaneous disorders

Diagnosis	No. of patients	No. with web
Iron deficiency anaemia	168	17 (10%)
Healthy controls	98	0
Pernicious anaemia	61	4
Ulcerative colitis	54	3
Thyroid disease	51	1
Miscellaneous	102	7
Total	534	32

The fact that only about 10% of patients with iron deficiency anaemia develop a web suggests that additional factors may be important in their pathogenesis, but few significant differences were noted when patients with post-cricoid webs were compared with a group of patients with iron deficiency but with no evidence of a web. The significant findings included an increased incidence in patients with a post-cricoid web of angular stomatitis and glossitis, confirming the association of a web and the other tissue changes associated with iron deficiency; three-quarters of the patients with webs were edentulous and it is of interest that edentia was also a feature in a series of patients with hypopharyngeal cancer (Wynder *et al.*, 1957). Thyroid disease was commoner in the patients with webs and suggested the possibility that autoimmune mechanisms might be operative in the pathogenesis of a web. Our attempts to detect a specific antibody reacting with pharyngeal tissue were unsuccessful but a number of auto-antibodies were present in patients with post-cricoid webs (Table 6), the only significant difference being the frequency of thyroid

cytoplasmic antibodies in patients with webs compared with the iron deficient control group. The gastric parietal cell antibody was frequent in both these groups when compared with the healthy controls.

TABLE 6. Incidence of autoimmune antibodies in post-cricoid web and controls

Antibodies	Post-cricoid web	Iron deficiency anaemia without web	Healthy controls
Thyroid cytoplasmic	28%	12%	5%
Thyroglobulin	21%	16%	11%
ANF	17%	15%	9%
Gastric parietal cell	25%	18%	8%
Smooth muscle	5%	7%	2%
Mitochondrial	0	<1%	0

Details of our six patients in whom a carcinoma of the upper alimentary tract developed after a post-cricoid web are shown in Table 7, together with results shown in three other series of patients with the Paterson-Kelly syndrome who have been followed for a variable period, the overall incidence ranging from 4 to 16%. When the rarity of post-cricoid carcinoma [5.2/million of the population (Jacobs, 1963)] is considered, the fact that nine of the total of 240 patients (3.75%) had a post-cricoid carcinoma represents a real increase in its incidence.

Several large retrospective studies of women with carcinoma of the upper alimentary tract have noted a high incidence of preceding long-standing dysphagia and iron deficiency anaemia (Ahlbom, 1936; Wynder *et al.*, 1957; Jones, 1961), but investigations prior to the diagnosis of the malignant condition have usually not been carried out and their association thus could be overestimated. The striking female preponderance in patients with post-cricoid carcinoma when compared to the rest of the gastrointestinal tract and the familial association between

TABLE 7. Association of Paterson-Kelly syndrome and carcinoma of the upper alimentary tract

References	No. studied	Duration of follow up	Site of carcinoma	Incidence %
Owen, 1950	34	15 years	Post-cricoid: 5	15
Shamma'a and Benedict, 1958	58	1-46 years	Buccal mucosa: 6 Oesophagus: 3	16
Jones, 1961	76	15 years in half	Post-cricoid: 1 Oesophagus: 1 Stomach: 1	4
Chisholm <i>et al.</i> , 1971a	72	Average: 6 years	Post-cricoid: 3 Oesophagus: 1 Piriform fossa: 1 Stomach: 1	8

iron deficiency, post-cricoid webs and post-cricoid carcinoma observed in our own series as well as that of others, provides further evidence of a link between these conditions.

It can be concluded that the available evidence confirms the association between iron deficiency, post-cricoid webs and post-cricoid carcinoma, but the mechanism whereby iron deficiency brings about these changes is as yet unknown; genetic, environmental and perhaps immunological factors may also be important.

References

- AHLBOM, H.E. (1936) Simple achlorhydric anaemia, Plummer-Vinson syndrome, and carcinoma of the mouth, pharynx and oesophagus in women. *British Medical Journal*, **2**, 331.
- CHISHOLM, M., ARDRAN, G.M., CALLENDER, S.T. & WRIGHT, R. (1971a) A follow-up study of patients with post-cricoid webs. *Quarterly Journal of Medicine*, **40**, 409.
- CHISHOLM, M., ARDRAN, G.M., CALLENDER, S.T. & WRIGHT, R. (1971b) Iron deficiency and autoimmunity in post-cricoid webs. *Quarterly Journal of Medicine*, **40**, 421.
- ELWOOD, P.C., JACOBS, A., PITMAN, R.G. & ENTWISTLE, C.C. (1964) Epidemiology of the Paterson-Kelly syndrome. *Lancet*, **ii**, 716.
- JACOBS, A. (1963) Post-cricoid carcinoma: regional incidence in England and Wales. *British Medical Journal*, **2**, 1373.
- JACOBS, A. & KILPATRICK, G.S. (1964) The Paterson-Kelly syndrome. *British Medical Journal*, **2**, 79.
- JONES, R.F. (1961) The Paterson-Brown Kelly syndrome, its relationship to iron deficiency and post-cricoid carcinoma. *Journal of Laryngology*, **75**, Part I, 529; Part II, 544.
- OWEN, R.D. (1950) The problem of hypopharyngeal carcinoma. *Proceedings of the Royal Society of Medicine*, **43**, 157.
- SHAMMA'A, M.H. & BENEDICT, E.B. (1958) Esophageal webs. A report of 58 cases and an attempt at classification. *New England Journal of Medicine*, **259**, 378.
- WALDENSTRÖM, J. & KJELLBERG, S.R. (1939) Recent genologic diagnosis of sideropenic dysphagia (Plummer-Vinson syndrome). *Acta Radiologica*, **28**, 618.
- WYNDER, E.L., HULTBERG, S., JACOBSSON, F. & BROSS, I.J. (1957) Environmental factors in cancer of the upper alimentary tract. *Cancer (Philadelphia)*, **10**, 470.