SIDEROPENIC DYSPHAGIA

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It has been well known for many years that glossitis and dysphagia may occur in association with chronic iron-deficiency anaemia. In Scandinavia the condition has been found to be especially common and cases have been described in which there have been marked changes in the oesophagus due to iron deficiency, but no anaemia.[1, 2] This unusual presentation, however, has been only rarely noted in the English literature,[3] and for this reason the present case is reported in detail.

CASE RECORD

The patient was first seen in June 1957. She was a married female aged 43 years who had come to South Africa from Holland 8 years previously. Her major complaints were difficulty in swallowing and soreness of the tongue, both of which had been present for 20 years. The symptoms had become worse in the preceding 3 months and the dysphagia was particularly troublesome. Both solids and liquids seemed to stick at the level of the cricoid cartilage and the dysphagia was so marked that the patient was forced to spend 1–2 hours over each meal. Vomiting was not a feature but food sometimes regurgitated into the mouth and she often woke at night to find her mouth full of saliva. Although the appetite remained good the dysphagia caused the patient to restrict her diet to soup, milk, occasional vegetables but no meat. On this diet the weight remained stationary for years at 127 lb., but in the few months before examination she had lost 8 lb.

Over the years the patient had consulted several doctors because of the dysphagia. In 1939 a diagnosis of 'nerves' was made; at that time she was told she was anaemic but no blood tests were done and no specific treatment was given. In 1946 her first child was born; she remained well during the pregnancy and there was no excessive postpartum haemorrhage.

In 1953, when she was in a maternity hospital for her second confinement, a hypochromic anaemia was diagnosed (haemoglobin 5·2 g.%). To the patient's knowledge there had never been any abnormal blood loss. Menstruation had always been normal and she had never vomited blood or passed it *per rectum*. In view of the low haemoglobin level she was given 4 pints of blood. At the time of discharge from the maternity hospital the haemoglobin had risen to 13·2 g.% and she received no further treatment.

In February 1956, an ear, nose and throat surgeon reported spasm at the level of the cricopharyngeus muscle on oesophagoscopy and this was said still to be present on barium swallow when she was re-examined in September 1956. The constriction was dilated with temporary relief of the dysphagia for about 2 weeks. Several blood tests were done during 1956; these showed persistently normal values, with haemoglobin levels varying between 13·3 and 16·3 g.%. In spite of this a short course of oral iron was given but the patient noticed no real improvement while on treatment. She was seen again in June 1957 by another physician. The haemoglobin level was 15·4 g.% and she was referred to the Johannesburg General Hospital for further investigation.

On examination she appeared a healthy, well-balanced woman. The main positive features were marked koilonychia and glossitis. The tongue appeared raw and beefy with atrophy of the papillae. Nothing else abnormal was noted on physical examination.

Special Investigations. Haemoglobin 17·0 g.%, haematocrit 52%, white blood count 4,000 per c.mm., film appearances normal. Sedimentation rate (Wintrobe) 3 mm. in 1 hour. Serum iron 93 gamma %, total iron-binding capacity 405 gamma %. Bone-marrow examination showed normoblastic erythropoiesis and no visible haemosiderin granules in unstained marrow particles and in specimens stained with Prussian blue. Plasma proteins 6·6 g.% (albumin 3·1, globulin 3·5). Blood urea 28 mg. per 100 ml. Gastric analysis showed no free acid present in fasting specimens, but after Kay's 'augmented histamine test'[4] (0·4 mg. per kg. given subcutaneously with 50 mg. of intramuscular mepyramine maleate) 13 c.c. of N/10 HCl in 100 c.c. of gastric juice. Absorption of radio-active B12 (measured as the amount excreted in a 24-hour specimen of urine when a 'flushing' dose of 1,000 micrograms was given 2 hours after the radio-active one) 17% (normal range 10–30%). Urine analysis normal. Stool examinations showed no occult blood.

On barium swallow (Fig. 1*a*) a stricture of the upper oesophagus

was shown projecting into the lumen mainly from the anterior wall in the manner of a web. On deglutition the oesophagus above the constriction bulged out to form a pseudo-diverticulum or pouch. In the anterior position, barium from both pyriform fossae was diverted across to the left and the stricture was again shown about 1½ inches below the crico-pharyngeus. For a short distance below this the oesophagus appeared narrowed and slightly irregular.

Technical Note on Radiological Examination. A web may easily be missed on routine examination and specialized technique was used for the barium-swallow examination. The method was to count aloud up to 'five' after having instructed the patient to swallow as large a bolus of barium cream as possible with a single swallowing movement at the count of 'two'. The passage of barium was then observed in order to assess the best time to expose a radiograph of the distended pharynx with the next mouthful. For such a study a rapid-acting spot-filming device is essential and the exposure should be not greater than 1/10 second if a sharp radiographic image is to be obtained.

Progress

Because of the severity of the dysphagia an oesophagoscopy was performed before treatment was begun. There was marked narrowing of the upper oesophagus. Above this the pharyngeal mucosa appeared normal. The constriction was then gently dilated. Although the mucosa felt roughened beyond the constriction no actual neoplasm was visualized. A biopsy specimen was taken from the mucosa distal to the constriction. Histologically the submucosa appeared slightly oedematous, with small round-cell infiltration, but there was no evidence of malignancy. The oesophageal dilatation caused prompt relief of the dysphagia and the patient was able to consume a normal diet without discomfort.

In hospital the iron stores of the body were replenished by a course of intramuscular iron (Imferon), a total of 1,600 mg. being administered. A follow-up barium swallow while the patient was still in hospital showed some improvement (Fig. 1 b). An anterior web was again shown about 1½ inches below the crico-pharyngeal sphincter but the lumen of the oesophagus below it was much broader and more easily seen. A small posterior web was also visualized slightly below the upper one. The oesophagus below the level of the web was demonstrated by a double contrast manoeuvre. It showed narrowing for a short distance but the surface appeared smooth.

Follow-Up

After discharge from hospital the patient was seen regularly at monthly intervals. She remained in good health for 6 months, experiencing no difficulty with swallowing. A repeat barium swallow 3 months after discharge showed that most of the objective improvement had been maintained, although the lumen was slightly narrower than on the previous study (Fig. 1c). Similar findings were made at a further examination in January 1958. The patient had by this time gained 10 lb. in weight and was feeling well. Moreover the tongue was no longer sore and regeneration of papillae could be seen. On odd occasions some dysphagia was experienced, especially with meat, but on the whole she was able to eat a full diet without difficulty. At this check-up another oesophagoscopy was carried out and the stricture was dilated again.

DISCUSSION

The association of iron-deficiency anaemia with glossitis and dysphagia has been described as the Plummer-Vinson syndrome. The condition is especially common in Sweden, where Waldenström and Kjellberg[1] reported its incidence as twice that of oesophageal carcinoma. It was at first thought that the dysphagia was either due to hysterical spasm[5] or to a derangement of the nerve plexuses.[6, 7] However, it has now been established that the dysphagia is associated with organic changes in the oesophagus.[8-10]

On radiological examination the most striking feature is a web which occurs in the upper part of the oesophagus between the level of the cricoid plane and the suprasternal notch. It is seen as a thin membranous shadow extending from the anterior wall of the oesophagus into the barium-distended lumen.[11-15] In severe cases it is more extensive and encircles the oesophageal lumen as a narrow ring structure[15] (Fig. 1). Sometimes a segment of narrowed oesophagus may be seen extending about ½ inch below the web, with occasionally a second web present at the lower limits of the narrowed area.[14] When the web is sufficiently extensive it can be seen in antero-posterior views as a localized narrowing

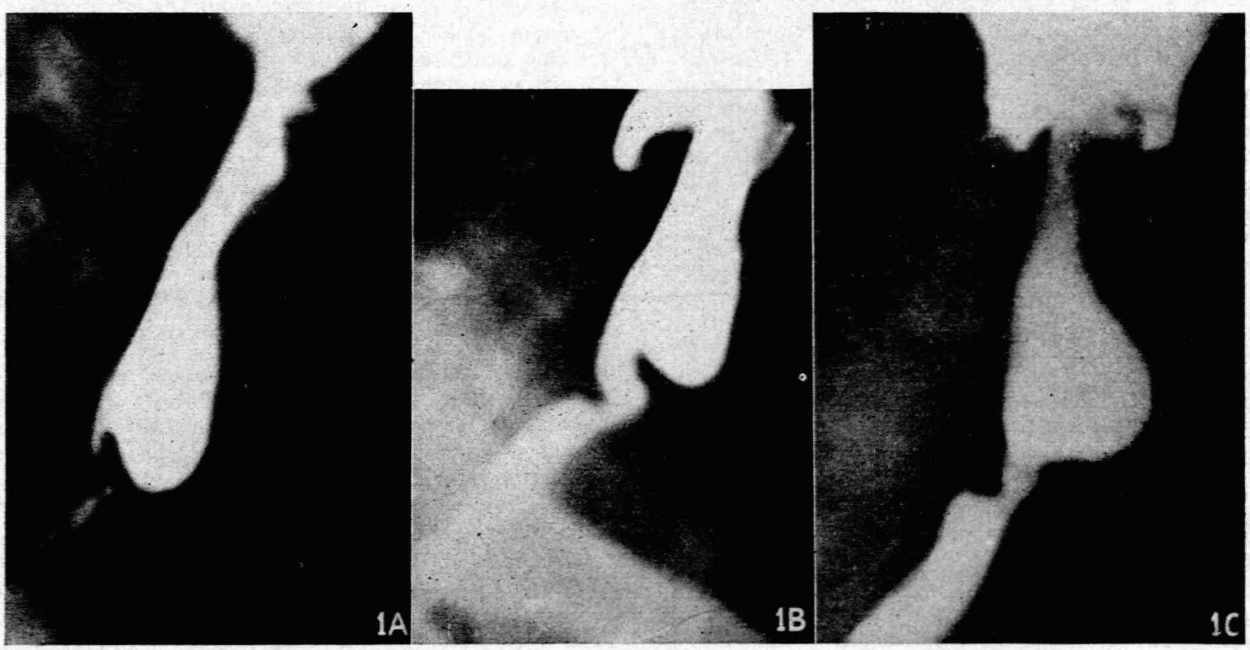

Figure 1*a*. Initial barium swallow, demonstrating the severe web stricture, with oesophageal dilatation above. *Figure* 1*b*. Barium swallow soon after oesophageal dilatation, showing the anterior and posterior webs. *Figure* 1*c*. Upper oesophageal film several months after dilatation. The changes are still present, but not as severe as before therapy.

of the distended oesophagus. If the degree of obstruction is marked, the barium bolus may cause the pharynx and oesophagus above the constriction to bulge out and the appearances may simulate a pouch (Fig. 1a). The differential diagnosis is usually not difficult since the radiological findings are quite unlike those of carcinoma and indentations of the oesophagus caused by anterior cervical osteophytes. The condition most likely to be confused with a web is spasm of the crico-pharyngeus.[19] However, the indentation by the muscle is posterior and is usually broader than a web.

Very little is known of the histological changes found in the Plummer-Vinson syndrome. In a case which came to autopsy Suzman[8] found hyperkeratinization of the oesophageal epithelium with areas of atrophic degeneration, while Hoover[9] reported that a web removed by punch biopsy consisted of two layers of mucous membrane separated by a small amount of fibrous tissue. More recently Savillahti[10] found localized atrophy and chronic inflammatory changes in the epithelium of a case which came to autopsy, and atrophic changes were noted in the muscular coat.

Although there was at first some dispute about the significance of the oesophageal changes found in states of iron deficiency there is no doubt now that they are caused by a depletion of tissue iron. Waldenström,[1] in 1937, was one of the first to stress the fact that iron deficiency can lead to widespread epithelial changes. He considered koilonychia, glossitis, achlorhydria and oesophageal webs as all manifestations of deficiency of tissue iron. He therefore proposed the term 'sideropenic dysphagia' as a rational way of describing difficulties in swallowing due to iron deficiency. In the past 2 decades iron metabolism has been extensively studied and the results have done much to confirm Waldenström's thesis. A consideration of this work is necessary in order to understand the proper significance of sideropenic dysphagia and to formulate a rational therapy.

There are about 4 g. of iron in the body of a normal adult male. The major portion is in the form of haemoglobin, but iron is also present in myoglobin, in the plasma, and in tissue enzymes. In addition, 1-1.5 g. are contained in the stores of the body.[16] Once introduced into the body, the iron is used again and again, with the result that only small amounts are normally absorbed and excreted at any one time. This, however, is less true in the female, where losses are normally incurred through menstruation and pregnancies. When such losses become excessive or when the diet is inadequate the iron balance may become negative. In such circumstances a fixed sequence of events occurs.[17] At first iron is mobilized from the stores to satisfy the needs of the bone marrow. When the stores have been depleted the level of iron in the plasma drops and finally anaemia develops. At first the anaemia is normocytic but, with growing deficiency in available iron, haemoglobin synthesis becomes impaired and a microcytic, hypochromic anaemia develops. It is at this stage that signs of epithelial damage usually develop. However, not all cases with epithelial changes manifest anaemia and although reports of such cases are rare in the English literature[3] they have been well documented by Scandinavian workers.[1, 2] In these cases the iron deficiency is often reflected by the finding of a low plasma-iron level. Metabolically it seems very probable that patients with sideropenic dysphagia and no anaemia are precariously balanced at a point where the stores are totally exhausted but enough iron is available from the breakdown of red-cells to satisfy the needs of the bone-marrow. In this state of delicate equilibrium, haemoglobin synthesis takes top priority, with the result that even the modest needs of the tissues are not met.

The case reported here appears to be an excellent example of such a metabolic upset. At the time she was first seen she had been complaining of symptoms for 20 years. The haemoglobin level was normal, but there was atrophic glossitis, koilonychia and marked dysphagia. Fasting achlorhydria was also present, but some acid secretion was produced with the 'augmented histamine test'[4] and the absorption of vitamin B12 was normal. Although the plasma-iron level was not lowered, no storage iron could be demonstrated in the bone-marrow specimen. It was known that she had suffered from a severe microcytic hypochromic anaemia 3 years previously at the birth of her second child. At that time she was given blood transfusions which restored the haemoglobin level to normal, but were apparently not sufficient to satisfy the tissue needs. The epithelial symptoms therefore continued to progress and 3 years later the glossitis and dysphagia were the presenting symptoms.

In mild cases it has been found that oral iron therapy causes prompt amelioration of the dysphagia. Although subjective relief is usually obtained, the radiological findings may show little change, a fact which suggests that spasm may play a part in the production of symptoms.[14] In severe cases it is usually necessary to dilate the oesophagus before starting treatment with iron. In the past it has been customary to use oral iron. Although such therapy is very effective in returning the haemoglobin level to normal it is extremely difficult to replenish body stores by the oral route.[18] There thus seems to be an excellent case for using parenteral iron in the treatment of the condition. In the present patient the iron-dextran complex, Imferon, was given intramuscularly with good results. It should be emphasised that the changes in the oesophageal epithelium have been shown to be pre-malignant by a number of authors,[1, 10, 13, 14] and the high incidence of hypopharyngeal and upper oesophageal carcinoma in Scandinavian women may well be due to the prevalence of sideropenic dysphagia in this area.[13] All cases *must* therefore be given adequate iron therapy; this means enough to correct anaemia, when present, and to refill the iron stores (i.e. an extra 1,500 mg.). In addition, every patient suffering from sideropenic dysphagia should be examined radiologically at 6-monthly intervals. Any irregularity of the oesophageal lumen above or below the web should be regarded with suspicion and investigated further.

SUMMARY

A case is described where iron deficiency caused marked epithelial changes (glossitis, oesophageal stricture and koilonychia) but no anaemia. Dysphagia, which was the most prominent symptom, was treated by oesophageal dilatation and intramuscular iron therapy with good results.

The diagnosis of sideropenic dysphagia is discussed and the pathogenesis of the condition is briefly outlined.

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REFERENCES

1. Waldenström, J. and Kjellberg, S. R. (1939): Acta radiol., **20**, 618.
2. Waldenström, J. (1946): Acta med. scand., suppl., **170**, 252.
3. Henderson, I. D. (1954): Lancet, **1**, 493.
4. Kay, A. W. (1953): Brit. Med. J., **2**, 77.
5. Vinson, P. P. (1922): Minnesota Med., **5**, 107.

6. Kelly, A. B. (1919): J. Laryng., **34**, 285
7. Paterson, D. R. (1919): *Ibid*., **34**, 289.
8. Suzman, M. M. (1933): Arch. Intern. Med., **51**, 1.
9. Hoover, W. B. (1935): New Engl. J. Med., **213**, 394.
10. Savillahti, M. (1946): Acta med. scand.. **125**, 40.
11. Mosher, H. P. (1917): Surg. Gynec. Obstet., **25**, 175.
12. Mosher, H. P. 1935): *Ibid*., **60**, 403.
13. Welin, S. (1953): Brit. J. Radiol., **26**, 218.
14. Hutton, C. F. (1956): *Ibid*., **49**, 81.
15. Waldman, H. K. and Turnbull, A. (1957): Amer. J. Roentgenol., **78**, 567.
16. Bothwell, T. H. and Finch, C. A. (1957): Amer. J. Dig Dis., **2**, 145.
17. Coleman, D. H., Stevens, A. R. and Finch, C. A. (1955): Blood, **10**, 567.
18. Finch. S., Haskins, D. and Finch, C. A. (1950): J. Clin. Invest., **29**, 1078.
19. Thomas, R. Glyn (1957): S. Afr. Med. J., **31**, 91.