Relationship of Plummer-Vinson Disease to Cancer of the Upper Alimentary Tract in Sweden

Lars-Gunnar Larsson, Anita Sandström, and Per Westling

Department of Oncology, University Hospital of Umeå, 901 85 Umeå, Sweden

Summary

Sideropenic anemia with epithelial lesions (Plummer-Vinson syndrome) was previously very common among women in northern Sweden. The incidence of this condition is decreasing, however, because of better nutrition and improved health care. Plummer-Vinson syndrome as a sequel of previous sideropenic anemia still influences the pattern of hypopharyngeal and oral cancer in northern Sweden, where the female/male ratio in these diseases is remarkably high and where cancer in the postcricoid part of the hypopharynx is relatively common. In Sweden as a whole, a decreasing trend in the incidence of hypopharyngeal cancer in women can be demonstrated, which is probably due to diminished prevalence of Plummer-Vinson syndrome.

Primary sideropenic anemia is a disease with many names. It is usually described by 2 attributes; the 1st attribute (primary, essential, idiopathic) demarcates the disease from sideropenic anemia with etiology, such as bleeding, infections, rheumatoid arthritis, and malignant growths; the 2nd expresses some characteristic laboratory finding (hypochromic, microcytic, sideropenic, achlorhydric). Waldenström (31, 32) proposed the name "essential sideropenia," as he found cases with characteristic epithelial signs and low serum iron but without anemia. This condition, with the epithelial lesions that often accompanied it, was previously very common in the northern parts of the world, and in some rural parts of northern Sweden it was almost endemic (22, 24, 32). The epithelial lesions described were brittle nails, koilonychia, glossitis, papillary atrophy of the tongue, oral fissures, a small mouth with narrow lips, a smooth facial skin, achlorhydria and atrophic gastritis, and postcricoid dysphagia with formation of webs or strictures in the lower part of the hypopharynx or the upper part of the esophagus (Plummer-Vinson or Paterson-Kelly syndrome). Some of these signs could appear rather rapidly, while the more atrophic and degenerative changes certainly required a long-standing sideropenic anemia for their development.

Primary sideropenic anemia of clinical importance and especially its epithelial complications have become less frequent because of improved nutrition, better health service and maternal care, and a decreasing number of pregnancies. The market has long been flooded with iron and vitamin tablets and tonics. Nutrition has improved also in rural and previously poor districts, and in some countries (as in Sweden) iron and vitamins are added to the flour. In Sweden, compulsory addition of iron to the flour was introduced in 1944. A young woman with sideropenic epithelial lesions as Plummer-Vinson's disease is today a rarity even in northern Sweden. What we still see is middle-aged or old women with persisting Plummer-Vinson syndrome, but their hematological disease was long ago cured by iron medication and adequate diet. This is probably the reason why some authors have suggested that the relation between sideropenic anemia and Plummer-Vinson syndrome might be only coincidental (10, 28). The relation between these 2 conditions is, however, well documented by many authors (6, 7, 22, 31, 33, 34, 37). Nevertheless, the true pathogenesis of "sideropenic" epithelial lesions and Plummer-Vinson syndrome is still obscure. Iron deficiency is certainly important but there are probably also other factors involved. Iron deficiency in tropical regions does not seem to give rise to the peculiar epithelial signs observed in Scandinavia, the United Kingdom, and the United States, and it has not been possible to induce similar lesions in laboratory animals with an iron-deficient diet (1). Other nutritional deficiencies (riboflavin, thiamin, pyridoxine, proteins) have been suggested (15, 16, 23, 36, 37), and it is obvious that hereditary factors are of importance also (22). Riboflavin deficiency causes very similar epithelial lesions in both human and animals (23). It is well documented that, in the rural areas of northern Sweden, where sideropenic epithelial syndrome was so common, the diet was nutritionally inadequate; this was especially true during the long winter seasons, when fresh vegetables and fresh meat and fish were not available, thus leading to deficiencies in iron and in some vitamins, such as ascorbic acid, riboflavin, and thiamin (24, 36, 37). It is possible that Plummer-Vinson syndrome has a complicated nutritional etiology, which could explain its peculiar geographic distribution.

Plummer-Vinson Syndrome

Postcricoid dysphagia combined with hypochromic anemia was first described about 1920 by Plummer (26) and Vinson (30) in the United States and by Paterson (25) and Kelly (20) in the United Kingdom. Plummer-Vinson or Paterson-Kelly syndrome is, however, not a strictly defined condition. The name is sometimes used for all the epithelial signs from the upper alimentary tract that may accompany...
hypochromic anemia, whereas in a more restricted sense, it is reserved for cases with postcricoid dysphagia and the rather typical roentgenological changes found in the hypopharynx or the upper part of esophagus. The latter definition is used in this article. Waldenström and Kjellberg (33) suggested the name “dysphagia sideropenia,” because they found a low serum iron to be a more constant finding than anemia. Today “dysphagia post-sideropenia” might be even more adequate, since almost all patients seen have only sequelae from a previously passed hematological and nutritional disorder.

The anatomical lesions found in the lower part of the hypopharynx or the upper part of the esophagus have been described by several authors from autopsy and biopsy material (11, 14, 17, 27). Webs and strictures have been found and the microscopic changes were characterized by fibrosis, epithelial atrophy, and epithelial hyperplasia sometimes combined with chronic inflammation. Epithelial changes of precancerous type have also been found.

The characteristic roentgenological findings were first described by Waldenström (31) and Waldenström and Kjellberg (33) in Sweden in 1938 to 1939. The findings consist of 1 or more webs in the lower part of the hypopharynx or the upper part of the esophagus, and sometimes a more or less pronounced stricture develops. Advanced changes are easily detected, but small webs require a special technique with good expansion of the hypopharynx by the barium contrast medium; such small lesions are nowadays best visualized by cinematographic technique. Small webs may be found even in patients without subjective dysphagia. As a rule, more advanced lesions cause severe distress, and every ear, nose, and throat department in northern Sweden has a small group of old Plummer-Vinson patients coming regularly for dilation of their strictures. In early cases the dysphagia is often remarkably improved by iron medication (6, 31), but in more advanced cases the lesions seem to progress even when the hematological disease is cured.

The frequency of Plummer-Vinson syndrome in sideropenia and sideropenic anemia will naturally be largely influenced by selection factors. It was, however, much less common than some other epithelial symptoms, such as brittle nails, angular stomatitis, glossitis and papillary atrophy, and achlorhydria. In a series of primary hypochromic anemia cases from northern Sweden, Lundholm (22) found Plummer-Vinson syndrome in about 19% of the cases. In a similar series from England, Beveridge et al. (7) found dysphagia in 9% of the women and in none of the men.

Relation to Cancer

That postcricoid dysphagia could be a precancerous condition was early suggested by Paterson (25) and Kelly (20). The relation of cancer in the upper alimentary tract to sideropenic anemia and Plummer-Vinson syndrome was, however, first documented by Ahlbom in 1936 (2–4). He noted that many patients with carcinoma of the hypopharynx and oral cavity, especially women, seen at Radiumhemmet in Stockholm had pronounced signs of sideropenic anemia and often of Plummer-Vinson syndrome. He also observed that the female/male ratio in these types of cancer was remarkably high in Sweden, and that hypopharyngeal cancer with postcricoid location was especially common among women. His observations have since been confirmed by several authors (5, 7, 12, 13, 18, 19, 21, 29, 34, 35, 37). Jacobsson (18, 19) analyzed a large number of cases of hypopharyngeal and tongue cancer in Sweden seen during the 1930's and 1940's and found also a remarkably high female/male ratio. He stated that, in hypopharyngeal carcinoma, 90% of the women and 10% of the men showed definite signs and symptoms of sideropenia. In women with carcinoma of the tongue, the corresponding figure was 35%.

Wynder et al. (37) performed an extensive study based on interviews of cancer patients from the middle and northern parts of Sweden. They drew the conclusion that the high incidence of cancer in the upper alimentary tract in Swedish women could be accounted for, at least in part, by the greater prevalence of Plummer-Vinson syndrome among women in Sweden.

Does the Incidence of Pharyngeal and Oral Cancer in Sweden Change?

Wynder et al. (37) suggested that improved nutrition might reduce the future incidence of cancer in the upper alimentary tract of Swedish women. Food habits and general health service have improved considerably in Sweden during the last 2 to 3 decades. At present no essential difference may be found between different parts of the country, and severe nutritional deficiencies must be rare. Because sideropenic epithelial lesions were quite common even up to the 1950's, it might be too early to observe a significant influence on the cancer incidence.

We have, however, looked through the available mortality and morbidity statistics. Unfortunately, the Swedish Cancer Registry did not start until 1959, and we have reliable incidence data only from 1960 to 1970 (8). In mortality statistics, cancer was pooled in 1 large group up to 1950. From 1951, however, cancers in the oral cavity and the pharynx were registered as a separate group (9). This group probably contains nasopharyngeal cancer also, but since this tumor is fairly rare in Sweden it should not

![Chart 1. Mortality in Sweden from cancer of the oral cavity and pharynx, 1951 to 1972. — , primary causes of deaths; ---, primary and secondary causes of deaths. (Before 1965 only primary causes of deaths were registered in the official mortality statistics.)](chart1.png)
The age distribution was fairly similar in men and women for both hypopharyngeal and oral carcinoma (Table 1). The female/male ratio was remarkably high, 1.0 in hypopharyngeal and 1.2 in oral carcinoma compared to 0.74 and 0.78 for the country as a whole.

Most men were smokers, and tobacco chewing was especially common among men with oral carcinoma. Smoking was not common in the female groups but, unfortunately, information about tobacco habits was lacking in many of the female records despite otherwise detailed histories. This is probably because smoking is so uncommon among middle-aged and old women from the rural parts of northern Sweden that it was considered unnecessary or almost insulting to ask about it (Table 2).
Among the women with hypopharyngeal cancer, 22 had obvious histories and 14 had suspected histories of sideropenia, hypochromic anemia, or epithelial sideropenic lesions; the corresponding figures for those with oral cancer were 8 and 15. Thus, roughly 75% of the female hypopharyngeal cancer patients and 25% of the female oral cancer patients showed sideropenic signs or symptoms. In the former group, 20 had obvious Plummer-Vinson syndrome and 3 had suspected Plummer-Vinson syndrome; in the latter group, 5 had obvious Plummer-Vinson syndrome and 2 had suspected Plummer-Vinson syndrome. Sideropenic symptoms and Plummer-Vinson syndrome were rare among the male patients, but they occurred in some men with hypopharyngeal cancer (Table 3). Hypopharyngeal changes of Plummer-Vinson type were in some cases diagnosed before the onset of tumor symptoms (Fig. 1). In some patients with carcinoma in the upper part of the hypopharynx, a typical postcricoid web could be noted at the time of admission (Fig. 2), and in a couple of patients it was demonstrated when the carcinoma had regressed after radiation treatment (Fig. 3). Typical hypopharyngeal changes were also seen in some patients with oral cancer (Figs. 5 and 6). Lingual changes were quite common among the female patients, but only rarely were they as pronounced as is illustrated in Figs. 4 and 5a.

In Table 4 the location of the tumors is listed. As expected, hypopharyngeal cancer was most often located in the upper part of the hypopharynx in men and in the lower part (postcricoid) in women. It was also obvious that a low location of hypopharyngeal cancer was correlated to the occurrence of sideropenic signs and symptoms (Table 5).

In oral cancer the most striking difference between men and women concerned gingival carcinoma. Cancer in the upper gingiva was more common in the male group and cancer in the lower gingiva was more common in the female group. Hypothetically, this might be explained by the habit among men of putting chewing tobacco in the upper oral vestibulum and by chronic trauma from ill-fitted dentures in women. Women in northern Sweden previously, as a rule, lost their teeth very early and the lower denture is more often ill fitted than is the upper one.

**Discussion**

It seems obvious that the previously very common epithelial lesions that accompanied sideropenic anemia still influence the pattern of cancer in the upper alimentary tract in northern Sweden. The picture is most clear-cut as regards hypopharyngeal carcinoma, which in Sweden probably has 2 main etiological factors, smoking in men and Plummer-Vinson syndrome in women. It will be very interesting to follow the incidence and pattern of this disease in Sweden.
now, when primary sideropenic anemia has diminished in frequency and is treated early. Already, a clear decrease in the incidence of this tumor among women can be noted.

The situation regarding oral cancer is far less clear. The incidence of this cancer seems to increase slowly both in men and women in Sweden, and the female/male ratio has not changed significantly. Smoking and tobacco chewing are probably very important factors for men but not for women. Plummer-Vinson syndrome is probably of importance and may explain the higher female/male ratio in northern Sweden, but the incidence of this syndrome is much lower in oral cancer than in hypopharyngeal cancer. Chronic trauma from dentures may be a factor of etiological importance, and Swedish women, especially in rural areas, usually lose their teeth much earlier than men do. This may also have been a result of iron deficiency or other nutritional deficiencies. In Table 6 the probable etiological factors in oral and hypopharyngeal cancer in Sweden and their possible relative importance are listed. The speculative nature of this table must, however, be emphasized.

References

Plummer-Vinson's Disease

Fig. 1. Woman, age 71, with long-standing history of sideropenic anemia, angular stomatitis, brittle nails, dysphagia and postcricoid hypopharyngeal stricture. One-half year before admission, pronounced roentgenological changes of Plummer-Vinson type (a and b). On admission, extensive hypopharyngeal carcinoma involving both upper and lower part (c). Pronounced papillary atrophy of tongue, plane nails. Hemoglobin and serum iron normal.

Fig. 2. Woman, age 61, with a history of fragile nails and angular stomatitis. No known anemia or dysphagia before onset of tumor symptoms. Large exophytic carcinoma in upper part of hypopharynx (pyriform sinus and lateral wall). Typical postcricoid Plummer-Vinson web below the tumor region. Normal hemoglobin and serum iron.

Fig. 3. Woman, age 63. Sideropenic anemia, Plummer-Vinson syndrome, and achlorhydria diagnosed 20 years before admission. On admission, large postcricoid hypopharyngeal carcinoma (a) and pronounced papillary atrophy of tongue; hemoglobin, normal; serum iron, 30 µg/100 ml. Roentgenograms taken 15 months after radiation treatment revealed postcricoid web of Plummer-Vinson type (b and c).

Fig. 4. Woman, age 72. History of long-standing sideropenic anemia and postcricoid dysphagia. On admission, postcricoid hypopharyngeal carcinoma, angular stomatitis, glossitis, papillary atrophy of tongue, and a small benign squamous cell papilloma on the left border of tongue. Hemoglobin and serum iron, normal.

Fig. 5. Woman, age 74. Pronounced sideropenic anemia with brittle nails diagnosed 20 to 25 years before admission. Increasing dysphagia for 5 to 7 years. No smoking, no syphilis. On admission, 2 separate oral carcinomas located to left and right side of mandibular gingiva. Thick leukoplakia covering a large part of the tongue, pronounced mucosal atrophy on other parts (a). Slight postcricoid stricture in hypopharynx (b and c). Hemoglobin and serum iron, normal.

Fig. 6. Woman, age 72. Sideropenic anemia and Plummer-Vinson syndrome diagnosed soon after puberty. Repeated dilations of hypopharynx. On admission, squamous cell carcinoma on right bucca, plane brittle nails, and rhagades in corner of mouth. Typical roentgenological Plummer-Vinson changes (a and b). Hemoglobin, 12.3 g/100 ml; serum iron, 48 µg/100 ml.
Plummer-Vinson’s Disease

3a
3b
3c
4

NOVEMBER 1975

Downloaded from cancerres.aacrjournals.org on April 13, 2017. © 1975 American Association for Cancer Research.
Relationship of Plummer-Vinson Disease to Cancer of the Upper Alimentary Tract in Sweden

Lars-Gunnar Larsson, Anita Sandström and Per Westling

Cancer Res 1975;35:3308-3316.

Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/35/11_Part_2/3308

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.