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Seventeen Patients with Peutz-Jehgers Syndrome in Four Generations

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THE Peutz-Jehgers syndrome is a familial disease characterized by abnormal melanotic pigmentation of the lips and oral mucosa associated with polyposis of the gastrointestinal tract.

Hutchinson [1] in 1896 reported the cutaneous manifestations of this disease by describing a peculiar deposit of melanin pigmentation on the lips of identical twin girls, which he considered a dermatologic curiosity. Fifteen years later Weber [2], his associate, reported that one of the twins had died from intestinal intussusception. Neither author was aware of the association between dermal pigmentation and intestinal polyposis.

Peutz [3] in 1921 described three generations of one family in which there were seven proved and three suspected cases of intestinal polyposis associated with the melanotic pigmentation of the lips and oral mucosa. Thus the familial pattern of this disease was established, but it remained for Jehgers to demonstrate that the "hereditary peculiarity" was carried as a mendelian dominant characteristic [4]. This conclusion was supported by the fact that in the majority of those possessing the necessary factor the typical syndrome developed. There were no skip generations, and both sexes of all ethnic groups were equally affected. This indicates a high degree of penetrance.

Bartholomew and associates [5] established the genetic features of the disease by tracing the hereditary pattern through a large "Harrisburg family" and by correlating their find-

ings with those of other investigators. This classic treatise dealt with 182 patients having the Peutz-Jehgers syndrome. Apparently the disease occurs more frequently than was understood.

The melanotic pigmentation, which appears on the lips and oral mucosa, has been aptly described as "black freckles." As a rule the lesions are discrete, measuring 2 to 5 mm. in diameter, but occasionally they coalesce to cover the entire surface of the lips. Sometimes they assume a cutaneous circumoral pattern as well. In rare instances they cover the cheeks and nose forming a "butterfly" configuration. The pigmentary deposits are not painful, indurated, hairy, or unduly vascular. Infrequently the spots appear on the palms of the hands, the soles of the feet, and in the interdigital web spaces. These cutaneous lesions may not be present at birth but appear during adolescence and may disappear with advancing age. The labial and mucosal lesions, however, are present at birth and persist throughout life.

The second feature of this entity, namely, intestinal polyposis, is rarely encountered in infants but appears during puberty or adolescence. The adenomatoid tumors are generally found in the jejunum, less frequently in the ileum, occasionally in the duodenum, and rarely in the stomach or colon. Early observers thought these polyps to possess malignant potentials, but recent studies fail to substantiate this thesis. Wenzel et al. [6] state, "Although malignancy has been reported in at least fifteen cases, there have been no documented reports of death by malignancy and no metastasis." Dormandy [7] suggests that mitotic figures are frequently seen in these

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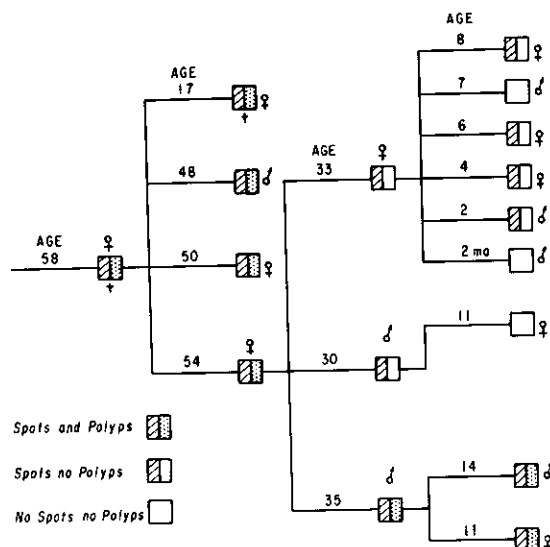


FIG. 1. Four generations of persons with the Peutz-Jehgers syndrome.

adenomas and are similar to the mitotic figures seen in the mucosa of normal healthy small bowel, and hence do not represent malignant transition.

Unfortunately, gastric and duodenal polyps do not always exhibit this benign tendency. Since 1963 six patients having the Peutz-Jehgers syndrome have died from generalized carcinomatosis, the primary focus being gastro-duodenal lesions [8].

The genetic pattern of the material exhibited in our study is that of a family consisting of seventeen members followed through four generations. (Fig. 1.) Intussusception due to polyps occurred in each generation. All members of the first, second, and third generations have the typical pigmentary changes of the lips. In the fourth generation there were nine children, five of whom have the typical pigmentary pattern whereas four have no such changes.

The clinical expression of this disease can best be described by actual case presentation.

CASE REPORTS

CASE I. A seventeen year old freckle-faced boy having fiery red hair was admitted to the hospital on September 15, 1946 complaining of intense abdominal pain. Vomiting was projectile and continuous. He had experienced previous attacks which had been relieved by ingestion of bicarbonate of soda. During these episodes his family stated, "His intes-

tines rumbled so loudly the noise could be heard in an adjoining room."

The medical student who wrote the history described the spots on the lips, oral mucosa, palms of both hands, and interdigital web spaces as "black freckles."

The entire abdomen was found to be distended, tympanitic, and very tender. A distinct tubular mass could be palpated in the right lower quadrant of the abdomen. Roentgenologic examination confirmed the diagnosis of acute intestinal obstruction.

When the abdomen was opened, 25 cm. of ileum was found to be involved in an incarcerated intussusception. This required segmental resection of the involved intestine. The excised specimen contained two benign adenomatoid polyps. Two additional polyps were found in the upper part of the jejunum. These were removed by segmental resection.

On May 11, 1951 this man was readmitted to the hospital with a second episode of intestinal obstruction. Again a large tubular mass could be palpated in the periumbilical region. When the abdomen was explored, it was apparent that intussusception was caused by a large adenomatoid polyp of the ileum. The involved bowel was gangrenous; hence, 70 cm. had to be resected. Palpatory examination revealed the presence of other polyps in the jejunum, but the patient was in such serious condition that further surgery was contraindicated.

On June 4, twenty-two days after the previous exploration, his third intestinal obstruction developed. His condition was so precarious that 6 feet of terminal ileum was exteriorized and double-barreled enterostomy was performed. The devitalized segment of ileum contained five degenerating benign adenomas. When his condition had sufficiently improved, a fourth operation was performed. At this time three polyps were removed from the jejunum by enterotomy. The exteriorized bowel was returned to the abdomen after anastomosis to restore intestinal continuity.

In August 1965 he was admitted for the fourth time because of exsanguinating hemorrhage from the bowel. At this time the hematocrit determination was 23 mm. and the hemoglobin level was 8 gm. Gastric aspiration recovered large quantities of red blood, and roentgenologic examination outlined a penetrating ulcer on the posterior wall of the duodenum. It was thought that vagotomy and pyloroplasty with ligation of the bleeding artery would be the only desirable procedure which could be performed and not produce nutritional malfunctions. It must be remembered that only 6 feet of the small bowel were intact. When this operation was performed, the remaining intestine was found to be free of polypoid formations.

CASE II. On June 11, 1964, the fourteen year old son of the patient in case I was admitted to the hos-



FIG. 2. CASE II. Hypertrophy and dilatation of jejunum secondary to partial obstruction of small bowel in a fourteen year old boy.

pital because of hypochromic anemia. Because melanotic spots were present on the lips and oral mucosa, the patient had been studied by gastrointestinal roentgenography since the age of five, but no polyps had been visualized. At admission, however, roentgenographic studies demonstrated high

grade obstruction of the jejunum, hypertrophy of its wall, and the presence of intraluminal polyps. (Fig. 2.) The radiologist was able to visualize reduction and recurring intussusception during fluoroscopy.

On surgical exploration the intussusception was found to involve 45 cm. of the jejunum and upper part of the ileum. The intestine was viable and the intussusception was easily reduced so resection was not required. The jejunum was opened and the polyp was excised. Further examination resulted in the detection of two more polyps which were removed by enterotomy.

In July 1966, two years later, progressive x-ray studies outlined one small polyp in the mid-portion of the ileum, but in the absence of symptoms of obstruction or bleeding the decision to follow a conservative plan of observation was made. He has remained asymptomatic.

CASE III. This is the thirteen year old daughter of the patient in case I. She too has typical melanotic pigmentation of the lips. Since the age of three years, she has had gastrointestinal x-ray studies every two years. It was not until 1964, at the age of eleven, that any polyps were found. At this time the jejunum harbored a large dumbbell-shaped polyp. (Fig. 3.) Because the child had no symptoms, it was elected to defer surgical treatment. Re-examination by roentgenography in July 1966 indicated intermittent obstruction and intussusception with dilatation and hypertrophy of the jejunum above the polyps. (Fig. 4.) When the abdomen was opened, we found three separate intussusceptions; two involved the jejunum and one was in the upper part of the



FIG. 3. CASE III. Dumbbell-shaped polyp without evidence of obstruction in an eleven year old girl.



FIG. 4. CASE III. X-ray film taken two years later showing "coiled spring" appearance of hypertrophied obstructed bowel caused by dumbbell-shaped polyp.

ileum. Each intussusception could be easily reduced, hence all four polyps were removed by incision of the bowel wall. All polyps were benign histologically, and recovery was uneventful.

COMMENTS

Despite the hereditary nature of the Peutz-Jehgers syndrome, the entity remains uncommon. In the past many persons in whom intussusception developed during adolescent life died, and hence they did not perpetuate the disease. Now, however, improved diagnosis and success of corrective surgery saves these patients, permitting them to transmit their hereditary defects. In 1955 Pool, Guice, and Farringer [9] searched the literature and found only thirty-nine authentic cases of this disease; however, in 1962 Bartholomew et al. [5] were able to collect the records of 182 patients having this syndrome. The increasing frequency of diagnosis is apparent.

When a physician encounters a patient with perioral pigmentary spots, he must search for concomitant intestinal polyps. The entire family should be alerted and instructed regarding the nature of the disease and the urgent necessity for continuous follow-up studies. Gastrointestinal roentgenograms should be taken every two years from the onset of puberty until full maturity in order to detect the presence of developing polyps. Insidious blood loss, massive hemorrhage, unusual borborygmus, and symptoms of small bowel obstruction certainly warrant careful observation and treatment. These polyps grow rapidly and often involve several segments of the intestine at the same time. Uncomplicated polyps can usually be removed by simple excision. If, however, intussusceptions have impaired the viability of the bowel, extensive resections may be required. It is important to remember that if the patient has attained full adult age and all tumors have been removed, additional polyps will not likely develop. On the other hand, if the polyps are not all removed, they may grow and cause serious complications in later life. In this family group we followed up three patients with known polyps for sixteen years. They refused surgery. One man had to be operated on at age forty-two because of intussusception and one woman required excision of an ileal polyp to control exsanguinating hemorrhage at age fifty-four. Accumulated experience indicates that lesions

of the jejunum and ileum are not malignant nor do they undergo malignant transition; hence, simple excision is the only treatment required. There has been no evidence of increased incidence of colonic or rectal cancer associated with the Peutz-Jehgers syndrome to this date. Dormandy [7] points out that members of an affected family who show no pigmentation of the skin or lips are extremely unlikely to have polyps develop or to transmit the characteristics to their offspring. Members of such a family who exhibit the pigmentary spots are likely to have polyps develop but are in no grave danger if they live near good medical facilities. This thesis is apparently correct in polyps distal to the ligament of Treitz, but gastric and duodenal polyps have shown an extremely high incidence of invasive and metastatic malignancy in young persons [8]. Anchor and Proctor [10] report the death of a thirteen year old girl who had oral pigmentation and polyps of the small bowel and colon and who died of infiltrating gastric carcinoma and metastases to the liver. Therefore, gastric or duodenal polyps require diagnosis and prompt surgical treatment if malignant transformation and metastasis are to be averted or controlled.

SUMMARY

The Peutz-Jehgers syndrome is a familial disease characterized by melanin pigmentation of the lips, oral mucosa, and skin associated with polyposis of the small intestine. The hereditary factor is a mendelian dominant characteristic and affects most members of the afflicted family regardless of sex. These polyps usually grow rapidly during the adolescent period, resulting in intussusception of the small bowel. Anyone exhibiting these pigmentary markings should have gastrointestinal x-ray studies beginning at age eight and continuing until adulthood is attained. Polyps in the jejunum and ileum can be removed by simple excision since polyps in these locations do not show malignant changes. Gastric or duodenal polyps, however, present a more serious problem until proved benign.

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Ten Year Survey of Oral Cancer in a General Hospital

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INSTITUTIONS in which significant numbers of patients with cancer are treated are obligated periodically to survey their results and to compare them to the achievements of other institutions. A survey of patients with oral cancer at the Yale New Haven Hospital is the subject of the present report. The hospital Tumor Registry maintains data for these patients in coded form on punch cards. An analysis of these cards was carried out covering the years 1951 through 1960. The status of all patients after a minimum of five years from diagnosis was established. It was, therefore, possible to compute all survival rates directly. Although standard errors are not reported, they may be easily computed by the reader if desired.† Some of the hospital charts were also reviewed. The present report can be compared with earlier reports from this institution, the first of which by Lawrence and Biezina [1] covered the years 1931 through 1940. A survey of cases of tongue cancer at Yale by Shedd, Schmidt, and Chang [2] included the years 1941 through 1955.

† The standard errors are $\sqrt{\frac{p(1-p)}{n+1}}$ where p is the proportion surviving and n is the number of patients in the cohort from which p is determined.

RESULTS

A total of 226 patients with oral cancer was

on record for the period 1951 through 1960. The diagnoses by sites and numbers were: tongue, eighty-four patients; floor of mouth, forty-five patients; mouth not otherwise specified, seventy patients (including alveolar ridges, buccal mucosa, and palate); tonsil, twenty-seven patients. Information on these sites is presented in detail.

Cancer of the Tongue. Of the eighty-four patients with lingual lesions, sixty-eight (81 per cent) were male and sixteen (19 per cent) were female. The age distribution is presented in Table I, where it can be seen that the majority of male patients were between the ages of fifty and eighty. Eleven of the sixteen female patients were of age fifty-nine or younger. Thirty-three of the lesions were of the base of the tongue, a location where the prognosis of lingual cancer is significantly poorer than in the anterior tongue. All of the patients were of the white race. All lesions were histologically confirmed as epidermoid carcinoma except for one lymphosarcoma. In nineteen patients (22.6 per cent) there was another cancerous lesion present at some time. In six of these, the second lesion was located in the upper aerodigestive tract, in one, in the lung, and in the remainder, in miscellaneous distant sites, rectum, prostate, and vulva. Sixty-five of the patients received their primary definitive treatment at this institution and nineteen were initially treated elsewhere. The "elsewhere" cases were of a more advanced stage of disease than the primary cases.

In Table II is presented the categorization of stage of disease at the time of diagnosis. One

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