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THE SYNDROME OF PEUTZ

INGRAM F. ANDERSON, M.B., B.CH. (RAND),* and ANTHONY J. LEONSINS, F.R.C.S. (EDIN.)

Department of Surgery, University of the Witwatersrand, Johannesburg

Peutz[24] first described the syndrome of familial gastro-intestinal polyposis, associated with mucocutaneous pigmentation, in 1921. However, it was not until its 'rediscovery', and masterly account of 10 patients suffering from the condition, by Jeghers *et al.*[18] that it received wider recognition. Since then, well over 100 cases have been recorded in the literature, but the syndrome is still poorly recognized and an estimate of prevalence is thus impossible. It has been suggested that it is probably at least as common as familial polyposis of the colon.[12] This report includes 2 members of a family affected with the syndrome.

CASE HISTORY 1

1st Admission

Mr. E., aged 29 years, was admitted to the Johannesburg General Hospital on 18 April 1947 with intestinal obstruction.

He gave a 4-year history of episodic, colicky, central abdominal pain accompanied by nausea and vomiting. Such attacks lasted for about an hour, otherwise he was perfectly well. There was an associated weight loss of 30 lb. over the preceding 3 years. The present episode began a week before admission, with frequent colicky spasms lasting about 5 minutes and with severe vomiting. He had passed no faeces or flatus for 2 days before admission.

On examination, he was a thin sallow European male, with kyphoscoliosis. The abdomen was distended and visible peristalsis was noted. No masses could be palpated. Rectal examination was negative. Straight X-ray examination revealed several fluid levels, and large-bowel obstruction was diagnosed. No comment was made about pigmentation.

At operation, an ileo-ileal and caecal intussusception was found, with a mass the size of an egg in the ileal lumen. The draining lymph glands were enlarged. Twelve inches of small gut containing the tumour were resected and an end-to-end anastomosis performed. The patient made an uneventful recovery.

The tumour was fleshy and irregular, and seedling growths were present at its base. The pathologist reported that the mucosal tissue exhibited considerable irregularity with some evidence of penetration of the underlying muscle, which at one point had extended almost to the serosa. The neoplasm had the histological features of a highly differentiated adenoma showing changes 'suggestive of early malignant transformation'.

2nd Admission

The patient did not return to follow-up clinic after the operation, but was re-admitted on 29 September 1953 with a history of 3 years of recurrent attacks of abdominal colic culminating in the present severe episode.

On examination (A.J.L.) he presented with signs and symptoms of a small-bowel obstruction with a definite mass in the right iliac fossa.

In addition, typical pigmentation was noted on the face, particularly around the eyes and mouth and also in the mucous membrane of the upper lip. The Peutz syndrome was considered as a diagnosis.

At laparotomy, a small-bowel volvulus at the ileocaecal junction was present with an intussusception containing 4 ileal polyps (Fig. 1). About 3 feet of small bowel were resected with adjoining enlarged mesenteric glands. End-to-end anastomosis was performed. Further definitive exploration was not undertaken.

Histologically, the tumours were typical adenomatous polypi with no evidence of malignancy.

* Now Medical Registrar, Department of Medicine, General Hospital, Johannesburg.

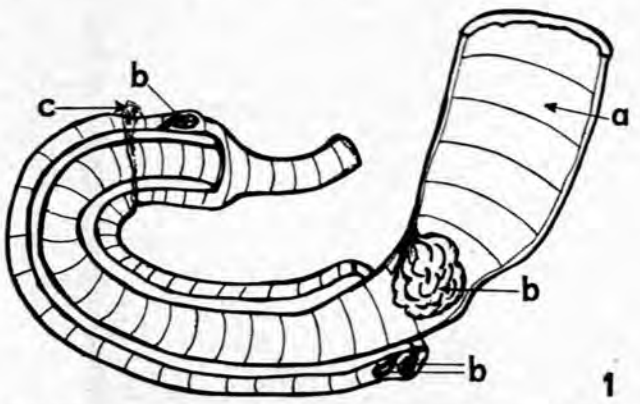

Fig. 1. Diagram showing findings at second operation (case 1)—a volvulus with intussusception containing 4 polypi. Note there is no polyp at the apex of the intussusceptum. (a= hypertrophied proximal bowel, b=1 large and 3 small polypi in the intussusception, c=fibrosis in previous anastomosis.)

3rd Admission

The patient was re-admitted on 15 February 1960 and one of us (I.F.A.) diagnosed sub-acute intestinal obstruction. The history was, as previously, of relief for about 2 years after operation, followed by the onset of recurrent abdominal pain. The pain was colicky and was now located in the right iliac fossa where a swelling had been noticed during attacks. This pain came on typically only during activity and was accompanied by marked borborygmi; it usually remitted suddenly and spontaneously, with the passing of flatus. The colic had been associated with diarrhoea and vomiting. There was no blood in the stool. On examination there was a ventral hernia in relation to the first operation scar. No masses were palpable. Dorsal kyphoscoliosis was noted. The haemoglobin was 13 G. per 100 ml. and occult blood was present in the stool. Barium studies could not be performed at the time.

Fig. 2. Typical cutaneous pigmentation on eyelids and around the orbits—case 1.

Operation was performed by Prof. D. J. du Plessis. The stomach appeared free of polypi on palpation. The small bowel was systematically examined and was hypertrophied throughout its entire length. Commencing at the proximal jejunum and working distally, a total of 5 enterotomies were performed and 15 pedunculated polyps removed. Wherever the bowel was opened the mucosa had a cobble-stone appearance from numerous commencing pin-head polypi.

The mesenteric glands were not enlarged. Other abdominal viscera, including large bowel, were normal.

The patient made an uneventful recovery. Histologically the tumours were adenomatous polypi of normal small-bowel epithelium with no evidence of malignancy. A double-contrast barium enema failed to reveal any evidence of colonic polyposis.

Typical pigmentation was noted around the eyes and on the eyelids (Fig. 2). However, the pigmentation of the lips previously noted was absent on this admission, and there was no involvement of the buccal mucous membrane. A random biopsy of the mucous membrane of the inner aspect of the upper lip was taken and showed a significant increase of melanin in the epidermis and dermis (Fig. 3).

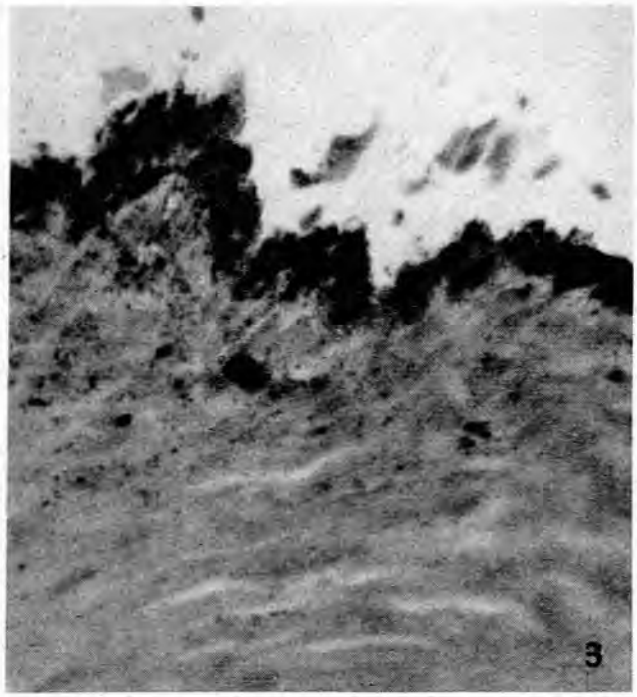

Fig. 3. Section of mucous membrane from upper lip showing increase in melanin in dermis and epidermis (silver stain for melanin)—case 1.

CASE HISTORY 2

The only child of the above patient, a daughter aged 5 years and 10 months, presented at the Transvaal Memorial Hospital for Children on 4 June 1956 with a history of intermittent rectal prolapse for 3 years. The mother had replaced this after stool, and laxatives had been used to prevent undue straining. Two years previously the family doctor had noted rectal polypi and cauterized these. During the 3-year period of rectal prolapse she had suffered from cramp-like abdominal pain and had passed red blood in the stool on a few occasions.

At the hospital barium-enema studies showed no convincing evidence of polyposis coli. At operation a grape-like mass of polypi was removed from the rectum and 2 smaller ones cauterized higher up. No note was made at the time of pigmentation, but the parents recall that she had had 'marks on her lips since she was a baby'.

We saw this child recently, now aged 10 years, and she displays typical pigmentation—around the eyes and mouth, and most strikingly on the lips and buccal mucous membranes (Fig. 4). has been having frequent episodes of abdominal colic and 9

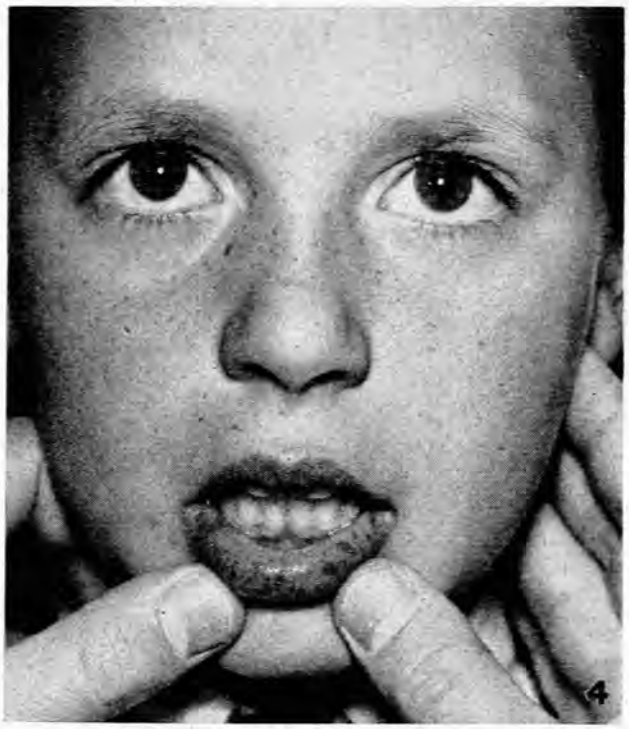

Fig. 4. Pigmentation of lips and peri-orbital region—case 2.

months ago had her appendix removed. We were unable to discover whether the appendix was acutely inflamed or not, but the persistence of cramps favours a diagnosis of intestinal polypi. Further examination of the child was not permitted.

DISCUSSION

The syndrome of Peutz has 3 cornerstones—heredity, polyposis, and mucocutaneous pigmentation.

Heredity

The polypi and the various forms of pigmentation are transmitted as Mendelian dominants[18] with a high degree of expressivity for both pigmentation and polyposis. The condition is heralded by pigmentation at birth or in early infancy. There is no particular racial or sex incidence.[3,28,30] The co-existence of 2 such apparently unrelated entities as polypi and pigmentation may be explained in several ways. Genetic linkage—the close association of 2 mutant genes—is untenable, because the 2 elements are seen apart too rarely for this. Pleomorphism is no longer a favoured explanation, but it is probable that the peccant gene has only a single action biochemically, many stages removed from the recognized clinical features.[23]

Various familial or congenital abnormalities have been reported in association with gastro-intestinal polyposis. Such an association may be purely coincidental or related to a general lowering of the phenotypic expression. A few patients with the Peutz syndrome have exhibited, in addition to the gastro-intestinal polypi, nasal and bladder polypi, and 1 patient had bronchial adenomatosis.[10,16,24] In view of the concept of 'visceral polyposis',[24] it is possible that the affected gene produces a disturbance at a critical stage of mucous-membrane development. Scoliosis has been noted by Tanner[33] and Dormandy[10] and was present in our adult patient. An

association with clubbing has been frequently noted,[9,18,20,26] while multiple skeletal malformations with soft-tissue tumours,[7] multiple bony tumours,[8] exostoses,[10] congenital heart disease,[10,18] diverticulitis and diverticulosis of the colon,[10] lateness of maturity,[18,20] and thyroid, adrenal and ovarian disease[6,8,18,33,35] have been reported less constantly. Pancreatic adenomatosis (Zollinger-Ellison syndrome) has been found in association with either pituitary, parathyroid or adrenal disturbance,[38] but has not been noted with intestinal adenomatosis.

Five genetic varieties of intestinal polyposis have been listed:[27] (1) Classical familial polyposis coli; (2) Peutz-Jeghers syndrome; (3) the Gardner syndrome (colonic polyposis associated with osseous and soft-tissue tumours); (4) the possible syndrome of Turcot, Deprés, St. Pierre (colonic polyposis and brain tumour); and (5) possible single isolated familial polypi.

Polyposis

The polypi are benign adenomata which may be sessile or pedunculated. They always arise in the small bowel, but may be found in the stomach or colon. They have not been described in the oesophagus. These polypi seem to erupt in different parts of the gut at different ages, with normal segments of gut intervening. Some polypi, notably those in the rectum, may undergo complete regression.[1] The majority of cases present with symptoms of gastro-intestinal polypi between infancy and middle age. Five of Dormandy's patients presented, several years before diagnosis of the full-blown syndrome, with rectal polypi in infancy, and this was well shown in our second case. Apart from the larger polypi, which can be removed, and the hundreds of pinhead growths which are seen at operation, Dormandy has stressed the existence of multiple intramural micro-adenomata in apparently normal-looking bowel. The common cause of obstruction is small-bowel intussusception, but the intussusception usually does not contain a polyp at its apex. The mechanism is probably local increase in peristalsis caused by micro-adenomata.

Histologically, the polypi give evidence of their origin from these intramural micro-adenomata by containing in their stroma interspersed thin and thick branching bands of muscularis mucosae. These bands are often dispersed among the glandular structures. The stroma may show infiltration with lymph, plasma and eosinophil cells. The normal glandular pattern of the small bowel is reproduced in the polypi (Fig. 5). This histological picture with the peculiar formation of the stroma and the reproduction of normal mucosal structure with multiple cell types has led to the belief that these polyps are developmental disturbances and are in fact hamartomas.[3,4,10,15,29] This same histological appearance may be interpreted as invasion of the muscular layer by the tumour and was probably responsible for many of the earlier diagnoses of malignant change. Our first case was diagnosed as showing an early malignancy of the small bowel, but review of the slide showed a typical adenomatous polyp. Several authorities agree that small-bowel polyposis in the Peutz syndrome is not precancerous.[10-12,32] There are two cases on record with undisputed carcinoma arising from a polyp.[2,5] Metastases have never been found arising from a polyp, nor have there been any reported deaths from carcinoma in the small bowel.[29]

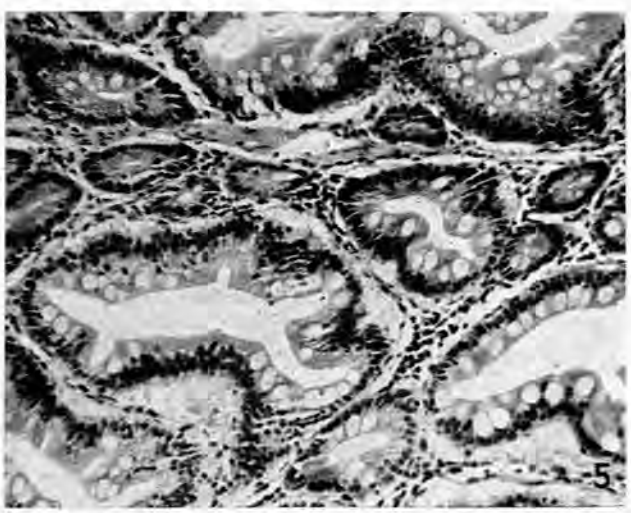

Fig. 5. Section of ileal polyp showing a normal glandular pattern with normal cells. Muscularis mucosae is seen branching between the glandular structures.

In contrast to the above, polypi in this syndrome, occurring in the colon and probably the stomach, are prone to undergo malignant transformation as often as any other polyp in this situation. A leading article in the *Lancet* put the matter nicely: There is something peculiar about the resistance of the human small bowel to malignancy. Its mucosa is extensive and it has a high mitotic rate. It lies in direct continuity with mucosae of the pylorus, bile ducts, pancreatic ducts, and colon—all areas of high cancer incidence.[14] Dormandy has commented on the apparent frequency of carcinoma of the rectum and colon in cases with the syndrome of Peutz.[13] We stress that, although the small-bowel polypi apparently do not tend to become malignant, those polypi in the colon and rectum must be regarded with great suspicion and be treated accordingly. It may be that a single pluripotential genetic error underlies both the Peutz syndrome and familial polyposis coli. Local factors in the colon, such as the end-products of digestion, may account for malignant change in the large-bowel polypi in both syndromes.

Pigmentation

The pigment is melanin and is probably present from birth. Cutaneous pigmentation occurs mainly around the facial orifices—mouth, nose, and eyes—and consists of small discrete round-to-oval macules not exceeding 3-5 mm. in diameter, with no tendency to coalesce. The colour varies from brown to black. Pigmentation has also been noted on the fingers, palms and toes, and more widely dispersed over the rest of the body.[25,33,40] The facial pigmentation usually fades during adolescence and may disappear altogether.[24] These spots must be differentiated from ordinary freckles, lentigo, chloasma, xeroderma pigmentosa, *cafe au lait* spots, and exogenous melanoses.

Histologically, the pigment has been described as occurring in vertical bands,[18] but most workers found no characteristic distribution.[10,31,34] Circumoral pigmentation without polyposis is not rare,[10,18,30,36] and familial polyposis without pigmentation has been noted.[17,39] Buccal mucosal pigmentation has been considered the *sine qua non* of the syndrome.[10,18] This was noted at first in our adult patient, but was strikingly

absent on his most recent admission, although a random mucous-membrane biopsy did show a significant increase in melanin (Fig. 3). The spots are about 5 mm. in diameter and are found on the lips, the buccal mucous membrane, hard and soft palate and nasal mucosa,[9] and more rarely the labial, conjunctival,[18] and rectal mucosae.[24] There is no pigmentation of the polyps, either in the small bowel or the colon.

Originally the syndrome was noted only in dark-haired, dark-complexioned patients,[18,33] but it does occur in fair-haired, light-complexioned people, although the pigmentation is then less obvious.[19,22,28] This is in accord with another family seen by one of us (A.J.L.) where the mother and 2 daughters with the Peutz syndrome were all fair-skinned.[21] Cases have not been reported in the Bantu.

DIAGNOSIS

Despite a family history and the presence of the characteristic pigmented spots, the condition is often misdiagnosed, as occurred initially in both our cases.

The patient usually presents with signs or symptoms of one or more of the following: (1) Intestinal obstruction; (2) bleeding and/or iron-deficiency anaemia; (3) intestinal hurry and malabsorption features; and (4) rarely with pigmentation.

Most commonly the patient is seen with enteric intussusception and obstruction. The clinical picture of the episodic colic, outlined previously, is so typical that a diagnosis can often be made on this alone. Overt rectal bleeding may be noted, but usually occult haemorrhage results in an iron-deficiency anaemia. Our young patient came to hospital with rectal prolapse. The increased peristalsis associated with polyposis may result in deficient absorption and stigmata of malnutrition. Rarely, the patients are seen at a dermatology outpatient department with a complaint of freckled 'dirty lips'.

Sigmoidoscopy and gastroscopy have limited diagnostic value and should be combined with double-contrast barium examinations of small bowel and colon.

TREATMENT AND PROGNOSIS

Surgical intervention may be life-saving but is never curative. Ultimately, cures will be achieved by correction of the underlying genetic biochemical disturbance.

With regard to the small bowel, treatment should be limited to symptomatic polyps and extensive resections are not advised.[10,12] In those cases with recurrent attacks, much depends on the frequency and severity of the episodes—if mild, simple measures may suffice. On the other hand, elective surgery may bring years of relief with minimal operative risk. Operation is carried out after adequate bowel preparation. A small incision is made on the antimesenteric aspect of the ileum about 25 cm. distal to the ligament of Treitz. Long Allis' forceps are inserted through this opening, and grip a full thickness of bowel wall as far away from the incision as possible. The forceps are then withdrawn and the bowel is intussuscepted through the incision. The mucosal surface may then be inspected under direct vision. About 20 cm. of gut on each side of the incision can thus be cleared of polyps—a total of about 10 enterotomies permits visualization of the whole small-bowel length.[37]

In polypi of the stomach, colon and rectum, malignant change is a distinct danger. Prophylactic surgery is indicated here, but 'cancer resections' are not justified prophylactically. Regular follow-up of these patients is imperative.

Overall life expectancy is not markedly reduced, and with careful supervision a reasonable prognosis is assured.

SUMMARY

A father and daughter affected by the syndrome of Peutz are presented.

The 3 main features of gastro-intestinal polyposis, mucocutaneous pigmentation, and heredity are discussed. The diagnosis is still too often missed and a wider recognition of the syndrome is called for.

The disappearance in later life of the typical mucosal pigment in the one patient is noteworthy.

The question of malignant transformation in the polyps is considered. The danger of such change occurring in the gastric or large-bowel area is stressed, and the necessity for prophylactic surgery and regular follow-up in these cases is emphasized.

Diagnosis and treatment are briefly alluded to.

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