Case report

Peutz-Jeghers syndrome and metastasising colonic adenocarcinoma

J H TWEEDIE, AND B G McCANN

From the Department of Surgery and Pathology, United Norwich Hospitals, Norwich, Norfolk

SUMMARY A case of metastasising colonic carcinoma associated with Peutz-Jeghers syndrome in a 39 year old man is described. The caecal adenocarcinoma had metastasised widely to regional lymph nodes and was associated with several other colonic Peutz-Jeghers polyps, showing no evidence of dysplasia or malignancy. It was not possible to determine whether the carcinoma had arisen from a Peutz-Jeghers polyp. The patient also had gastric and small intestinal polyps. The serum carcinoembryonic antigen (CEA) was normal at presentation in this patient and in one other reported case. The use of this determination as a screening test for so-called high risk groups is, therefore, not supported by this report. The risk of malignancy is not known. It will only be determined by careful follow up of a defined Peutz-Jeghers syndrome population and comparison of carcinoma incidence with a matched sample of the general population. A national registry of Peutz-Jeghers syndrome patients in the United Kingdom would help to resolve this question.

First described by Peutz in 1921,¹ and subsequently expanded by Jeghers, McKusick, and Katz in 1949,² this syndrome consists of the association of gastrointestinal polyps mucocutaneous pigmentation and a familial incidence. The polyps may occur throughout the gastrointestinal tract but are most frequently found in the small intestine. Initially there were conflicting views as to the frequency with which malignant changes occurred in the intestinal polyps and this was because of the misinterpretation of the histological structure of the polyp.³⁻⁴ The irregular arrangement of normal epithelium and smooth muscle derived from the muscularis mucosae in the polyp suggested malignant invasion to earlier investigators. The polyps are now considered to be hamartomas.⁴⁻⁶ There are well documented case reports of malignant change in the stomach,⁷⁻¹¹ gastroduodenal junction,¹² duodenum,⁸⁻¹³⁻¹⁶ small bowel,¹⁷⁻²⁴ and colon³⁻¹¹⁻²⁵⁻²⁷ in patients with Peutz-Jeghers syndrome, which has led to the suggestion that there is an increased liability to carcinoma of

the gastrointestinal tract. The familial occurrence of carcinoma in several of the reports also enhances the view of a genetic malignant trait.¹⁰⁻²⁵⁻²⁸ The exact risk is unknown, as is the incidence of Peutz-Jeghers syndrome in the general population. Moreover, two large series reviewing the risk of carcinoma in Peutz-Jeghers syndrome have reported conflicting results.¹¹⁻²⁹ This case is reported as it documents the occurrence of a metastasising carcinoma of the caecum in a patient with Peutz-Jeghers polyps of the colon.

Case history

A 39 year old white man was admitted on 21 January 1983, with a six month history of epigastric pain, weight loss of 8 kg and lassitude. He had had no previous episodes of abdominal pain. There was no family history of pigmentation, abdominal pain or rectal bleeding, although he had a 13 year old daughter with similar facial pigmentation.

On examination the patient was pale with pigmentation of the lips and about the eyes (Fig. 1). A firm, tender mass was palpable in the right side of the abdomen. Rectal examination disclosed fresh

Address for correspondence: Mr James H Tweedie, FRCS, Doctors' Mess, Derbyshire Royal Infirmary, Derby.

Received for publication 16 December 1983

Fig. 1 Photograph of patient showing typical Peutz-Jeghers pigmentation about the eyes and lips.

blood on the examining finger, but no masses.

Investigations showed a Hb of 8.5 g/dl, MCV 64 fl, MCH 18.8 pg, MCHC 29.4 g/dl. The ESR was 40 mm/h. The serum iron was 2.5 $\mu\text{mol/l}$. All other laboratory data, including glucose, blood urea nitrogen, uric acid, sodium, potassium, chloride, bicarbonate, calcium, phosphate, bilirubin, serum glutamic oxaloacetic transaminase, lactate dehydrogenase, alkaline phosphatase, albumin, globulins, and total serum proteins were normal. The serum carcinoembryonic antigen (CEA) on admission was normal (10 $\mu\text{g/l}$). At oesophagogastroduodenoscopy carried out on 22 January 1983, one small polyp was seen in the stomach and two larger ones in the duodenum. Sigmoidoscopy showed fresh blood within the lumen but no mucosal lesions in the rectum. Barium meal and follow through examination showed one polyp in the duodenum and suggested that there were further polyps in the small bowel. Barium enema and air contrast examination (Figs. 2 and 3) showed a large polyp in the descending colon and a smaller one in the ascending colon in addition to a large carcinoma of the caecum.

He was transfused 4 units of blood and underwent laparotomy on 14 February 1983. At operation 10 polyps, seven of them large, were felt in the small bowel. There was a 5×7 cm carcinoma in the caecum with small seedlings on the peritoneal surface of the ileocaecal mesentery and involved lymph nodes along the course of the superior mesenteric vessels and extending towards the hilum of the liver. Colonic polyps were also felt. Biopsies

were taken of the peritoneal secondaries and of the lymph nodes in the mesentery, one close to the tumour and one high up at the origin of the superior

Fig. 2 Double contrast barium enema. Large pedunculated polyp in descending colon (A). Histologically this polyp was a hamartoma with no evidence of dysplasia or malignancy (see Fig. 5).

Fig. 3 Double contrast barium enema. Carcinoma of the caecum (A), and polyp in ascending colon (B). Histologically the lesion (A) was a poorly differentiated adenocarcinoma and the polyp (B) a hamartoma with no evidence of dysplasia or malignancy.

mesenteric artery. All three showed adenocarcinoma (Fig. 4). The extent of disease made curative resection impracticable. The presence of peritoneal secondaries made prolonged survival unlikely and with the size, extent, and distribution of small bowel polyps it seemed unlikely that a palliative right hemicolectomy to control haemorrhage would succeed. Accordingly no further operative procedure was undertaken. He made an uneventful postoperative recovery. Because of persistent gastrointestinal blood loss and severe reactions to blood transfusions he was transferred to St Mark's Hospital (London) for colonoscopy. At colonoscopy, performed by Dr C B Williams on 23 March 1983, three polyps (2.5, 3, and 4 cm size) were removed by snare polypectomy, and the caecal carcinoma was biopsied. The colonic polyps were hamartomas (Fig. 5) showing no evidence of dysplasia or malignancy and the caecal carcinoma histologically confirmed as an adenocarcinoma.

A palliative right hemicolectomy was performed on 29 March 1983. He made an uneventful postoperative recovery. Histology of the right hemicolectomy specimen confirmed a poorly differentiated adenocarcinoma of the caecum. It was not possible to determine whether this had arisen from a hamartomatous polyp. Postoperatively he was started on a course of radiotherapy to the involved nodes and this was completed on 24 May 1983. After this he began adjuvant chemotherapy in the form of Adriamycin, Mitomycin C, and 5-Fluorouracil. His condition, however, gradually deteriorated and he died on 25 September 1983. No necropsy was performed.

Discussion

In a large review of patients with Peutz-Jeghers syndrome,¹¹ colonic polyps occurred in 53% and rectal polyps in 32%. The question of an increased risk of colorectal carcinoma in patients with Peutz-Jeghers syndrome and colonic polyps is thus very important. Part of the debate surrounding the malignant potential of Peutz-Jeghers polyps is centred on whether the Peutz-Jeghers polyps have undergone malignant transformation, or whether the malignancy has arisen coincidentally in a pre-existing adenomatous polyp. It is generally accepted that there is an adenomatous polyp/cancer sequence in the rectum and colon, although the majority of adenomas do not become cancerous during a normal adult life span.^{30 31} The hamartomatous nature of the colonic polyps in Peutz-Jeghers syndrome is well established.⁴⁻⁶ Adenomatous colonic polyps, however, have also been described in patients with Peutz-Jeghers syndrome^{28 32} and these last authors also mention the existence of hamartomas in the same patients. In addition, Perzin and Bridge²⁴ report a case of Peutz-Jeghers syndrome in which histology of a single duodenal polyp showed areas of hamartomatous and adenomatous cellular arrangement with *in situ* carcinoma. It was not possible to determine whether the *in situ* carcinoma had developed from the hamartomatous or adenomatous element of the polyp. Although invasive carcinoma has been shown to have arisen in Peutz-Jeghers polyps in the small bowel,^{8 21} there are no recorded cases where a colonic carcinoma has been unequivocally shown to have arisen from a Peutz-Jeghers colonic polyp. Areas of severe glandular dysplasia have been recently noted in a hamartomatous polyp removed from the colon of a 35 year old man with Peutz-Jeghers syndrome.³³ Other hamartomatous polyps removed from the colon at the same time showed no such dysplasia. These authors suggest that Peutz-Jeghers polyps are

Fig. 4 Photomicrograph of mesenteric lymph node removed at laparotomy showing invasion of the node with adenocarcinoma. (H & E original magnification $\times 150$).

proliferative and may be premalignant. Areas of severe dysplasia in a Peutz-Jeghers polyp removed from the rectum have also been described.⁸

In our case it was not possible to determine whether the carcinoma had arisen from an adenomatous or hamartomatous colonic polyp. Other polyps removed from the colon and small bowel at the same time were hamartomas with no evidence of dysplasia or malignancy. Although histological observations such as these are very important and provide good circumstantial evidence of the malignant potential of the polyps, the ultimate answer can only come from detailed prospective studies of a defined Peutz-Jeghers syndrome population and comparison of carcinoma incidence with a matched sample of the general population.

In a group of 21 patients with Peutz-Jeghers syndrome seen at the Mayo Clinic and followed up to 45 years (median follow up 33 years), there was no evidence of intestinal carcinoma arising from a hamartomatous polyp, with possibly one exception where it was impossible to tell whether the primary lesion was of colonic or ovarian origin.²⁹ In addition, there was no evidence of decreased survival when compared with a matched general population. In

contrast with a large national survey of 222 patients with Peutz-Jeghers syndrome in Japan, 11 (5%) patients with carcinoma of the colon were identified in the surveyed group.¹¹ The cause of death of eight patients was registered as caused by carcinoma of the colon. In six patients the diagnosis was histologically confirmed. Mortality was lower than in patients with familial polyposis coli, but higher than in the general population.

Clearly further prospective studies of this nature are needed to resolve the question of cancer risk. It is unlikely that the true incidence of the syndrome and the risk of malignancy will be established without a national registry.

This report and one other²⁵ both record normal CEA values at the time of presentation when the colonic carcinoma had already metastasised. The use of this determination as a screening test for carcinoma in patients bearing colonic polyps is therefore not supported by this report. This report endorses the conclusion of the NIH consensus statement³⁴ that the use of CEA to help with surveillance of so-called high risk groups in whom CEA producing tumours may develop remains to be established.

Fig. 5 Photomicrograph of colonic polyp removed at colonoscopy. The polyp shows the typical features of a Peutz-Jeghers hamartomatous polyp. The glands are irregular and the stroma is composed of branching muscularis mucosae (arrowed). There is no evidence of dysplasia or malignancy (H & E original magnification $\times 30$).

The authors would like to thank Mr I Ranger and Mr A Cameron for permission to report the case admitted under their care. The authors would also like to thank Drs B C Morson and H J R Bussey of the Pathology Department, St Mark's Hospital, London, for permission to publish the photomicrograph shown in Fig. 5, and for their advice in the preparation of the manuscript. The authors also gratefully acknowledge the help of Squadron Leader R A Stanley of Princess Mary's RAF Hospital, Halton, for furnishing details of the patient's treatment while under his care. We are grateful to Mrs Christine Russell for preparing the manuscript.

References

- 1 Peutz JLA. Very remarkable case of familial polyposis of mucous membrane of intestinal tract and nasopharynx accompanied by peculiar pigmentation of skin and mucous membrane. *Ned Tijdschr Geneesk* 1921; **10**: 134-46.
- 2 Jeghers H, McKusick VA, Katz KH. Generalised intestinal polyposis and melanin spots of the oral mucosa, lips and digits: a syndrome of diagnostic significance. *N Engl J Med* 1949; **241**: 993-1005 and 1031-6.
- 3 Bailey D. Polyposis of gastro-intestinal tract: the Peutz syndrome. *Br Med J* 1957; **2**: 433-9.
- 4 Bartholomew LG, Dahlin DC, Waugh JM. Intestinal polyposis associated with mucocutaneous melanin pigmentation (Peutz-Jeghers syndrome). Review of literature and report of six cases with special reference to pathological findings. *Gastroenterology* 1957; **32**: 434-51.
- 5 Rintala A. The histological appearance of gastro-intestinal polyps in the Peutz-Jeghers syndrome. *Acta Chir Scand* 1959; **117**: 366-73.
- 6 Morson BC. Some peculiarities in the histology of intestinal polyps. *Dis Colon Rectum* 1962; **5**: 337-44.
- 7 Achord JL, Proctor HD. Malignant degeneration and metastasis in Peutz-Jeghers syndrome. *Arch Intern Med* 1963; **111**: 498-502.
- 8 Cochet B, Carrel J, Desbaillets L, Widgren S. Peutz-Jeghers syndrome associated with gastrointestinal carcinoma. *Gut* 1979; **20**: 169-75.
- 9 Kopylow A, Bielecki M, Dominiczak K. The Peutz syndrome. *Pol Rev Radiol Nucl Med* 1963; **27**: 480-8.
- 10 Payson BA, Moungis B. Metastasising carcinoma of the stomach in Peutz-Jeghers syndrome. *Ann Surg* 1967; **165**: 145-51.

- 11 Utsunomiya J, Gocho A, Miyanga T *et al.* Peutz-Jeghers syndrome: Its natural course and management. *John Hopkins Med J* 1975; **136**: 71–82.
- 12 Horn RC, Payne WA, Fine G. The Peutz-Jeghers syndrome (Gastrointestinal polyposis with mucocutaneous pigmentation). Report of a case terminating with disseminated gastrointestinal cancer. *Arch Pathol* 1963; **76**: 29–37.
- 13 Gasser U, Arquint A. Ein Fall von Peutz-Jeghers Syndrom mit maligner Entartung. *Schweiz Med Wochenshr* 1969; **99**: 1894–5.
- 14 Reid JD. Duodenal carcinoma in the Peutz-Jeghers syndrome. Report of a case. *Cancer* 1965; **18**: 970–7.
- 15 Warren KW, Kane GA, Poulantzas JK. Peutz-Jeghers syndrome with carcinoma of the duodenum and jejunum. *Lahey Clin Found Bull* 1965; **14**: 97–102.
- 16 Williams JP, Knudsen A. Peutz-Jeghers syndrome with metastasising duodenal carcinoma. *Gut* 1965; **6**: 179–84.
- 17 de la Pava S, Cabrera A, Studenski ER. Peutz-Jeghers syndrome with jejunal carcinoma. *NY State J Med* 1962; **62**: 97–100.
- 18 Mackman S, Perna G, Gossett F. Peutz-Jeghers syndrome with metastases to an abdominal incision. *Arch Surg* 1969; **98**: 99–102.
- 19 Moretti G, Bozic C, Genton N. Polyposis familiale du type Peutz-Jeghers, avec degenerescence maligne. *Ann Chir Infant* 1969; **10**: 243–8.
- 20 Ryo UY, Rok SK, Balkin RB, Siedband LB, Sobel GW, Pinsky SM. Extensive metastases in Peutz-Jeghers syndrome. *JAMA* 1978; **239**: 2268–9.
- 21 Matuchansky C, Babin P, Coutrot S, Druart F, Barbier J, Maire P. Peutz-Jeghers syndrome with metastasising carcinoma arising from a jejunal hamartoma. *Gastroenterology* 1979; **77**: 1311–5.
- 22 Beinfield MS, Changus GW. Peutz-Jeghers syndrome. Report of a case of small intestinal polyposis and carcinoma associated with melanin pigmentation of the lips and buccal mucosa. *Gastroenterology* 1958; **35**: 534–9.
- 23 Kutscher AH, Zegarelli EV, Rankow RM, Mercandante JL. Peutz-Jeghers syndrome: follow up on patients reported in the literature. *Am J Med Sci* 1959; **238**: 180–6.
- 24 Perzin KH, Bridge MF. Adenomatous and carcinomatous changes in hamartomatous polyps of the small intestine (Peutz-Jeghers syndrome): Report of a case and review of the literature. *Cancer* 1982; **49**: 971–83.
- 25 Hsu S-D, Zaharopoulos P, May JT, Costanzi JJ. Peutz-Jeghers syndrome with intestinal carcinoma. *Cancer* 1979; **44**: 1527–32.
- 26 Humphries AL, Shepherd MH, Peters HJ. Peutz-Jeghers syndrome with colonic adenocarcinoma and ovarian tumour. *JAMA* 1966; **197**: 296–8.
- 27 Shibata HR, Phillips MJ. Peutz-Jeghers syndrome with jejunal and colonic adenocarcinoma. *Can Med Assoc J* 1970; **103**: 285–8.
- 28 Dodds WJ, Schulte WJ, Hensley GT, Hogan WJ. Peutz-Jeghers syndrome and gastrointestinal malignancy. *Am J Roentgenol Rad Ther Nucl Med* 1972; **115**: 374–7.
- 29 Linos DA, Dozois RR, Dahlin DC, Bartholomew LG. Does Peutz-Jeghers syndrome predispose to gastrointestinal malignancy? *Arch Surg* 1981; **116**: 1182–4.
- 30 Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975; **36**: 2251–70.
- 31 Lane N, Fenoglio CM, Haye GI, Pascal RR. Defining the precursor tissue of ordinary large bowel carcinoma: implications for cancer prediction. In: Lipkin M, Good RA, eds. *Gastrointestinal tract cancer*. New York: Plenum, 1978: 295–324.
- 32 Altmeier WA. In discussion: Dozois RR, Judd ES, Dahlin DC, Bartholomew LG. The Peutz-Jeghers syndrome: is there a predisposition to the development of intestinal malignancy? *Arch Surg* 1969; **98**: 509–17.
- 33 Yaguchi T, Wen-Ying L, Hasegawa K, Sasaki H, Nagasako K. Peutz-Jeghers polyp with several foci of glandular dysplasia. *Dis Colon Rectum* 1982; **25**: 592–6.
- 34 Carcino-embryonic antigen: Its role as a marker in the management of cancer. Summary of an NIH consensus statement. *Br Med J* 1981; **282**: 373–5.