Case 34

A 28-year-old Caucasian woman, who worked for the military, presented with a 12-month history of passing blood per rectum. Bright red blood was mixed in with the stool at almost every bowel motion. There was no blood on the paper or otherwise in the pan. Over the same period, her bowel habit had started alternating between being loose and constipated. She also reported occasional colicky abdominal pain, not related to opening her bowels. She had not lost any weight. She had no relevant past medical history or family history.

Examination of the abdomen was unremarkable. A digital rectal examination and proctoscopy revealed no abnormalities and no source of bleeding.

Investigations showed:

- Hb 7.7g/dL, MCV 58fL, platelets 485 x 10^9/L, ESR 29mm/hr
- Colonoscopy: a concentric, stenosing tumour at the hepatic flexure
- Histopathology showed a moderately differentiated adenocarcinoma with a large mucinous component and surrounding inflammatory infiltrate.

She was referred to a colorectal surgeon and oncologist for further investigation and appropriate management.

Questions

34a) Should rectal bleeding always be investigated?

34b) What is the best investigation for this patient?

34c) What should you tell the patient to expect regarding further investigation and management?

34d) What effects and side effects can the patient expect from adjuvant chemotherapy?

34e) Should family members be screened?

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Answers

34a) **Should rectal bleeding always be investigated?**

Bright red blood per rectum is a common symptom. In a survey of the general population in the UK, 20% of people between 20 and 80 years of age reported blood loss per rectum within the preceding 6 months. The most common cause is haemorrhoids, although this does not, of course, exclude more proximal pathology. Patients >50 years of age should best have full colonic imaging, either by colonoscopy or CT scanning (below).

The management of younger patients is subject to some debate. The American Society for Gastrointestinal Endoscopy guidelines (2000) state that colonoscopy is 'generally indicated' for patients with visible rectal bleeding. This is not universally accepted and practice varies, because the judicious allocation of resources needs to be balanced against the possibility of missing serious pathology.

A prospective cohort study of colonoscopy for investigating a history of visible rectal bleeding in 622 patients from Italy confirmed that colonic malignancy is very rare in patients <50 years of age. In the group of 312/622 patients <40 years of age, only 2/312 (0.6%) had a colonic malignancy (both were distal to the splenic flexure and in reach of a flexible sigmoidoscope). Diverticular disease was found in 11/312 (3.5%), and 10 (3.2%) had ulcerative colitis, both easily diagnosed by flexible sigmoidoscopy. Malignancy of the colon does, however, sometimes occur in young people. Diagnosis may be delayed as a consequence of a low index of suspicion, and this may be associated with a worse outcome. Concomitant iron deficiency anaemia in this young patient influences the choice of investigation (below). It is probable that tumour biology is different and more aggressive at a younger age.

34b) **What is the best investigation for this patient?**

It is clear that the risk of colorectal cancer in a 28-year-old patient without a family history of the condition is extremely low. There are, however, clinical points of note. The rectal bleeding was constant, with almost every bowel motion, mixed in with stool and not otherwise noticed in the bowl or on the toilet paper. This is not typical of anal canal bleeding. The fact that the blood was described as 'bright red' is an unreliable indicator of the distance of pathology from the anus. Furthermore, the patient reported intermittent colicky abdominal pain. Of most note, however, our patient had a profound microcytic anaemia. The elevated platelet count can be assumed to indicate either significant chronic blood

loss, or an acute phase response, both of which indicate serious pathology. The elevated ESR is more difficult to interpret, because red blood cells tend to sediment more quickly in the presence of anaemia.

Bright red rectal bleeding with normal proctoscopy, colicky abdominal pain, and microcytic anaemia requires thorough examination of the colon to confirm or exclude significant organic pathology. It is debatable whether the patient should have an upper gastrointestinal endoscopy as well to exclude villous atrophy associated with coeliac disease: this should generally be routine in patients with iron deficiency anaemia (see Case 38), but in the present case the rectal bleeding gives clear evidence of colonic pathology. **Colonoscopy** is the procedure of choice in this patient, because she is young and should be spared unnecessary radiation associated with CT colonography. Colonoscopy has the added benefit of enabling mucosal biopsy for histopathological diagnosis.

Colorectal imaging has, however, undergone a revolution in the past 5 years and colonoscopy should not be assumed always to be the default investigation.

The optimal technique depends on:

- Purpose of the investigation
- Most likely pathology (carcinoma, polyps, IBD, or telangiectasia)
- Age of patient, comorbidity, and available resources (waiting times).

Barium enema and flexible sigmoidoscopy

- *Advantages*: reliably images caecum; may be more available than colonoscopy; flexible sigmoidoscopy images the sigmoid colon.
- *Limitations*: colonoscopy still needed if a potential polyp is identified; adequate separation of sigmoid loops cannot always be achieved (hence need to be combined with flexible sigmoidoscopy). Barium enema may still miss polyps >1cm, although reliably (96%) identifies colorectal cancer. CT techniques and colonoscopy have made barium enema virtually obsolete in developed countries.

Flexible sigmoidoscopy

- *Advantages*: simple, safe procedure; usually performed without sedation after a phosphate enema without full bowel preparation; allows biopsies to be taken. Initial **procedure of choice** for assessing inpatients with diarrhoea (bloody or otherwise) and out-patients with distal colonic bleeding.
- *Limitations*: does not image the proximal colon.

Colonoscopy

- *Advantages*: gold-standard for colonic imaging at all ages except for the elderly or frail; allows therapeutic intervention.
- *Limitations*: lack of capacity to meet demand in many hospitals; potentially incomplete examination (caecal intubation rate may be 85–90%); risk of perforation (about 0.1%); need for bowel preparation (risk of potentially serious metabolic disturbance in elderly).

CT colon (also called minimal or long preparation CT colonography)

- *Advantages*: minimal preparation. Bowel preparation only needs a few millilitres of gastrograffin contrast over 3 days prior to procedure. Sensitivity is 85–90% for colorectal cancer. Initial colonic imaging **procedure of choice for elderly** or frail patients.
- *Limitations*: less sensitive than CT colonography or barium enema.

CT colonograpy (also called virtual colonoscopy/CT pneumocolon)

- *Advantages*: sensitivity as good as colonoscopy in trained hands. Initial colonic imaging **procedure of choice** in many centres for patients >45 years of age when the aim is to exclude cancer; provides some limited additional information from cross-sectional imaging of the whole abdomen; reduces the need for colonoscopy by 10–20%. The major advantage over barium enema is that there is no need for flexible sigmoidoscopy.
- *Limitations*: radiologist time to scrutinize scans (20–30min/scan); extracolonic pathology may not be detected, since intravenous contrast is not given routinely.

34c) **What should you tell the patient to expect regarding further investigation and management?**

Surgical resection is appropriate. She will need a **thoracoabdominal and pelvic CT scan** to stage the tumour and exclude metastases. MR scan of the abdomen is generally only needed as well for patients with rectal cancer, because it better defines pelvic anatomy than a CT scan. If imaging excludes metastases, resection of the primary tumour performed by a specialist colorectal surgeon using a **laparoscopic-assisted** approach, is the next step. Discussion about the surgical technique is done with the specialist colorectal surgeon, if laparoscopic expertise or equipment is not locally available, then a patient this young is usually best referred to

a specialist centre. The chance of needing a stoma with a tumour at the hepatic flexure is low.

The resected tumour is then further staged by histopathology. This is the most reliable predictor of long-term outcome. It forms the basis of decisions regarding adjuvant chemotherapy. Staging may be based on the **TNM (tumour-node-metastasis) staging** system or on the older **Dukes'** system (Tables 34.1–34.3). Adjuvant chemotherapy is generally offered to all patients following resection who are found to have stage III (node positive) disease (Dukes' stage C), if they are fit enough for a 6-month course of chemotherapy. Age has to be considered, because survival benefit from chemotherapy must be seen in the context of the patient's population-based life expectancy.

34d) **What effects and side effects can the patient expect with adjuvant chemotherapy?**

There is a modest, but clear survival benefit for patients with Dukes' C carcinoma of the colon who receive adjuvant chemotherapy. The absolute benefit for stage III (node-positive) disease is about 10% over 5 years for **5-fluorouracil** (5-FU)-based chemotherapy. The addition of **oxaliplatin** may add a further 5% absolute survival benefit in this group. Higher risk patients with node-negative disease and transmural (T4, Table 34.1) tumours, or presentation with bowel perforation or obstruction, may benefit more. Chemotherapy for stage II colorectal cancer is less well defined. Patients may have an absolute survival benefit of just 4% from 5-FU-based chemotherapy. Oxaliplatin has not been shown to add any benefit in these patients.

Therapy needs to be tailored to the individual and account taken of their views. 5-FU is usually administered for 5 days out of every 28 for a total of 6 cycles. The drug is given either as a daily bolus or a continuous infusion, and is administered with folinic acid (leucovorin). Side effects from bolus regimens include neutropenia, stomatitis, and diarrhoea, which are less common with continuous infusions. On the other hand, continuous infusions have a higher rate of hand and foot syndrome

Table 34.1 Dukes' classification of colorectal cancer

A	Tumour confined to the mucosa and submucosa
B	Tumour invading the muscularis propria (B_1=T2N0M0; B_2=T3N0M0)
C	With lymph node(s) involvement
D	With distant metastasis

Table 34.2 TNM staging for colorectal cancer

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into the subserosa
T4	Tumour directly invades other organs or structures, or perforates visceral peritoneum
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in 1–3 regional lymph nodes
N2	Metastases in 4 regional lymph nodes
Distant metastases (M)	
Mx	Presence or absence of distant metastases cannot be determined
M0	No distant metastases detected
M1	Distant metastases detected

(painful erythematous rash of the hands and feet), which is also the major side effect of capecitabine (an orally administered prodrug of 5-FU). Capecitabine has also been associated with severe secretory diarrhoea causing hypomagnesaemia and hypokalaemia. Oxaliplatin may cause paraesthesiae and a cumulative, dose-related peripheral neuropathy, which may be irreversible.

Table 34.3 Stage grouping and 5-year survival

Stage	TNM classification	Approximate 5-year survival (%)
I	T1–2, N0, M0	90
IIA	T3, N0, M0	80–85
IIB	T4, N0, M0	70–80
IIIA	T1–2, N1, M0	65–80
IIIB	T3–4, N1, M0	50–65
IIIC	T1–4, N2, M0	25–50
IV	T1–4, N0–2, M1	5–8

Our patient underwent a laparoscopic-assisted, extended right hemicolectomy. Histopathological staging showed a completely resected tumour with no affected lymph nodes, T3N0M0 (stage IIA, Dukes B_2). She received 6 cycles of capecitabine, which was well tolerated. Stage IIA colon cancer (T3N0M0) has a 5-year survival rate of around 80%, after resection with curative intent (Table 34.3).

34e) **Should family members be screened?**

Our patient had colon cancer diagnosed at 28 years of age. This implies an increased risk of colon cancer in first-degree relatives. Screening for family members should be instituted.

British Society of Gastroenterology (BSG) guidelines recommend that patients who have one first-degree relative diagnosed with colon cancer <45 years of age should have a full colonoscopy at the time of consultation for an indicative family history, or at 35–40 years of age, whichever is later. Further surveillance is guided by findings at the initial colonoscopy. If the first colonoscopy is normal, a second colonoscopy is recommended at 55 years of age.

American Gastroenterology Association (AGA) guidelines recommend that first-degree relatives of patients diagnosed with colorectal cancer at <60 years of age should have colonoscopy performed every 5 years, starting at 40 years of age or at an age 10 years younger than the index case. Our patient was 28 years old at the time of diagnosis. AGA guidelines imply initiation of screening colonoscopy in first-degree relatives at 18 years of age, and every 5 years thereafter, which many healthcare systems would feel too burdensome for the diagnostic return. Testing of the tumour for microsatellite instability with MSI analysis or loss of a mismatch repair gene is appropriate when colorectal cancer is diagnosed in young patients (see Case 17).

Further reading

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