Leukaemic lesions of the gastrointestinal tract

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SYNOPSIS This study is based on the clinical records and post-mortem findings of 264 patients with leukaemia. Gross leukaemic lesions in the gastrointestinal tract were found in 39 patients, an overall incidence of 14.8%. The incidence in all types of acute leukaemia was 18.4%, in chronic leukaemias 9.6%, and in myeloid leukaemia 10.9%. The ileum, stomach, and proximal colon were the sites most commonly affected. Four types of lesion were found: raised leukaemic nodules, leukaemic plaques, diffuse infiltrations with a convoluted brain-like appearance of the mucosal folds, and a multiple leukaemic polyposis. The clinical and pathological features of these lesions are described, and references are given to similar cases reported in the literature.

Although many case reports of leukaemic lesions in the gastrointestinal tract are available in the literature very little attempt has been made to determine the nature, incidence, and extent of these lesions or to assess their clinical importance.

Briquet in 1835, Virchow in 1856, and Boettcher in 1866 described gastrointestinal lesions which may have been due to leukaemia, but in the absence of blood studies the exact diagnosis of these cases remains uncertain. In 1892 Eichhorst described a case of fatal haematemesis due to gastric vein erosion by a deposit of acute myeloid leukaemia, and in the same year Hansemann described a case of fatal peritonitis in a patient with chronic myeloid leukaemia due to perforation of a leukaemic ulcer in the stomach wall. In 1894 Askanazy described a patient with acute myeloid leukaemia who had nodular and ulcerating lesions throughout the gastrointestinal tract. In 1905 Letulle and Halbron described a patient with chronic myeloid leukaemia who had leukaemic nodules in the mesentery and wall of the small intestine, the intestinal lesions being numerous and frequently pedunculated. Cases reported in the German literature have been reviewed by Herxheimer (1913), Singer (1922), Köhn (1951), and others, and cases reported in the French literature by Debray and Sarakinos (1958). So far as we are aware there is no comparable review of cases reported in the British and American literature.

There is considerable variation in the reported incidence of gross leukaemic lesions found in the gastrointestinal tract at necropsy. In Ikeda's (1931) study of 77 patients with leukaemia there were only three with gross lesions in the stomach, and in the series of 28 cases reported by Pearson, Stasney, and Pizzolato (1943) there were only two with gross lesions in the stomach or large intestine. Symmers (1948), however, found intestinal lesions in 14 out of 40 patients with lymphoid leukaemia, and Wahl and Hill (1956) found gastric lesions in seven out of 64 patients with all types of leukaemia. When macroscopic and microscopic involvement are considered together the reported incidence of leukaemic lesions in the gastrointestinal tract becomes even higher (Kirshbaum and Preuss, 1943; Paul and Hendricks, 1948; Naruki, 1958).

Very little attention has been paid to the clinical importance of these lesions, and the literature available contains a number of contradictory statements which do not appear to be supported by any clinical or pathological evidence. These findings led to our study of leukaemic lesions in the gastrointestinal tract and to our attempt at some assessment of their clinical importance.

MATERIALS AND METHODS

This study is based on 9,383 consecutive necropsies performed at the Postgraduate Medical School, London, between April 1935 and October 1960, and on 5,561 con-

secutive necropsies performed at the Westminster Medical School between January 1938 and October 1960. Amongst these 14,944 necropsies there were 264 cases of leukaemia. The post-mortem reports of these 264 cases were studied to find out the number of patients with gross leukaemic lesions in the gastrointestinal tract. The site, size, and general appearances of these lesions were recorded, and sections taken for histology were checked. A record was kept of associated lesions in the gastrointestinal tract such as peptic ulcer, erosions, non-specific ulceration, and carcinoma, and the cause of death was noted in every case. Clinical records were examined, and the number of patients with symptoms referable to the gastrointestinal tract noted. A separate record was kept of the nature, duration, severity, and time of onset of these symptoms, and an attempt was made to determine the cause of bleeding in patients with haematemesis and melaena.

The diagnosis of leukaemia was based on a study of peripheral blood films and bone marrow biopsies which were taken in every case, and as far as possible we have tried to eliminate all leukaemoid reactions. The classification employed corresponds with that given by Wintrobe (1956). For the sake of convenience the subacute and acute forms of leukaemia have been considered together, and the monocytic leukaemias include both the Naegeli and the Schilling types.

In our study of cases reported in the literature we have omitted reference to cases of lymphosarcoma in which a terminal leukaemic blood picture was seen. Lymphosarcoma cell leukaemia (leuko-sarcoma) and lymphatic leukaemia differ in their cytology, tissue culture appearances, immunology, clinical features, incidence, and prognosis, and there is increasing evidence, clinical and pathological, for a distinction between these two disorders (Hayhoe, 1960). We have also omitted reference to cases of pseudo-leukaemia. This term, coined by Cohnheim in 1865, has been used to describe patients with malignant tumours of lymphoid tissue who did not show leukaemic changes in the blood. Most of these cases are now recognized as lymphosarcoma, and only a few as possible examples of other disorders.

RESULTS

INCIDENCE OF LESIONS The number of patients with gross leukaemic lesions in the gastrointestinal tract is shown in Table I. The incidence in patients

Type of Leukaemia	No. of Patients	No. with Gastro-intestinal Lesions	Percentage of Patients with Gross Lesions
Acute myeloid	54	7	13.0
Acute lymphatic	48	7	14.6
Acute monocytic	32	9	28.1
Stem cell	13	4	30.8
Chronic myeloid	56	5	8.9
Chronic lymphatic	58	7	12.1
Plasma cell	2	0	—
Chronic monocytic	1	0	—
Total	264	39	14.8

with all types of acute leukaemia was 18.4%, in chronic leukaemias 9.6%, and in myeloid leukaemia 10.9%. The overall incidence in the 264 patients was 14.8%.

SITE OF LESIONS The sites of the gross leukaemic lesions found in the gastrointestinal tract are shown in Table II. The ileum, stomach, and proximal colon were the sites most commonly affected, and the duodenum and distal half of the colon the sites least commonly affected. The lesions were confined entirely to the stomach in nine cases, to the small intestine in 13 cases, and to the large intestine in seven cases. In seven cases extensive segments of the gastrointestinal tract were involved.

GASTRIC LESIONS Three types of gastric lesion were found: plaque-like thickenings of the stomach wall, raised nodular lesions, and diffuse infiltrations with a brain-like appearance of the gastric mucosa. Plaque-like thickenings of the stomach wall were found in nine patients. These plaques were usually solitary, their sizes varying from 0.5 to 8.0 cm. with the majority measuring more than 2.5 cm. in their maximum diameter. The plaques were mainly situated in the submucosa, but the underlying muscle coats were involved in seven cases and the overlying

Type of Leukaemia	Number of Patients with Gross Lesions in					
	Stomach	Duodenum	Jejunum	Ileum	Colon	Rectum
Acute myeloid	2	0	1	4	2	1
Acute lymphatic	0	0	0	6	2	0
Acute monocytic	3	1	3	6	6	3
Stem cell	3	1	0	0	1	1
Chronic myeloid	3	0	0	2	1	2
Chronic lymphatic	4	0	0	2	3	0
Total	15	2	4	20	15	7

FIG. 1

FIG. 1. *Stomach: diffuse infiltration by chronic lymphatic leukaemia producing a convoluted, brain-like appearance of the mucosal folds.*

FIG. 2

FIG. 2. *Diffuse leukaemic infiltration producing a gross dilatation of the stomach.*

mucosa was ulcerated in six. Raised nodular lesions were found in three patients. These nodules were small, multiple, and confined entirely to the mucosa and submucosa. Slight mucosal ulceration was seen in only one case. Diffuse infiltrations producing a convoluted, brain-like appearance of the gastric mucosa were seen in three patients with stem cell leukaemia, acute monocytic leukaemia, and chronic lymphatic leukaemia (Fig. 1) respectively. In two of these cases the stomach was grossly dilated (Fig. 2). The leukaemic infiltrations were situated in the mucosa and submucosa, slight involvement of the muscle coats and small areas of mucosal ulceration being seen in only one of the three cases examined.

INTESTINAL LESIONS Four types of intestinal lesion were found: plaque-like thickenings of the intestinal wall, raised nodular lesions, diffuse infiltrations with a brain-like appearance of the intestinal mucosa, and polyps. Plaque-like thickenings of the intestinal wall were described in eight patients. These leukaemic plaques were seen equally in the small and large intestine, were usually multiple, and varied in size

from 0.5 to 6.0 cm. with the majority measuring more than 3.0 cm. in their maximum diameter. Mucosal ulceration was found in five cases (Fig. 3), and muscle coat involvement in four. Raised nodular lesions were described in 21 patients. In 17 cases numerous tiny nodules were seen, varying in size from 0.5 to 1.0 cm. In four cases large solitary nodules, varying in size from 4.0 to 6.0 cm., projected into the lumen of the bowel. Mucosal ulceration was found in nine and muscle coat involvement in seven of these 21 patients.

One patient, under the care of Mr. Harold Dodd, had diffuse leukaemic infiltrations producing a convoluted, brain-like appearance of the intestinal mucosa. This patient, a man aged 79, had chronic lymphatic leukaemia, and at necropsy diffuse leukaemic infiltrations were seen in the stomach, duodenum, and sigmoid colon (Fig. 4). The diffuse infiltrations were confined to the mucosa and submucosa, and only slight infiltration of the muscle coats was seen (Fig. 5).

Another patient, a man aged 39, with subacute myeloid leukaemia, had leukaemic polyps through-

FIG. 3. *Jejunum: ulcerated plaques of acute myeloid leukaemia.*

out the large intestine. The post-mortem description of the large intestine (Prof. I. Doniach) refers to an . . . 'extraordinary thickening of its wall all the way from the caecum to the rectum. The thickening was due to submucosal deposits which had raised the overlying mucosa to form apparent polyps. These varied in diameter from a few millimetres to 1 cm., and were extraordinarily numerous. In addition to these polyps there was a gross oedema of the submucosa. The lesion was present in the rectum but not so marked as higher up'.

PEPTIC ULCERS Peptic ulcers were found in 13 patients, eight occurring in the stomach and five in the duodenum. Eight cases were associated with myeloid leukaemia, three with monocytic leukaemia, and two with lymphatic leukaemia. These ulcers have been considered in detail elsewhere (Cornes, Jones, and Fisher, 1961a).

GASTRIC EROSIONS Gastric erosions associated with petechial haemorrhage in the stomach wall were found in 19 patients. Eighteen patients had acute leukaemia, and one had chronic myeloid leukaemia.

NON-SPECIFIC INTESTINAL ULCERATION Ten patients had non-specific ulceration of the small or large intestine. The large intestine was affected in six cases and the small intestine in four cases. Nine patients had acute leukaemia, and one patient had chronic myeloid leukaemia.

ANAL LESIONS Four patients had extensive anal ulceration, and one patient had a large ischio-rectal abscess. Histological sections from three patients with anal ulceration were available for study. These showed thrombosed blood vessels with necrosis and sloughing of the overlying tissues. No leukaemic infiltration was seen. Two of these three patients had acute monocytic leukaemia, and one patient had chronic lymphatic leukaemia.

MISCELLANEOUS LESIONS One patient with acute myeloid leukaemia had monilial ulceration of the oesophagus, stomach, and ileum. One patient with chronic lymphatic leukaemia had a small fibroma in the proximal ileum. One patient with plasma cell leukaemia had an associated adenocarcinoma of the ascending colon.

FIG. 4

FIG. 4. *Sigmoid colon: diffuse infiltration by chronic lymphatic leukaemia.*

FIG. 5. *Sigmoid colon: diffuse infiltration of mucosa and submucosa by chronic lymphatic leukaemia. Haematoxylin and eosin ($\times 6$).*

FIG. 5

SYMPTOMS Although most patients gave a history of anorexia, nausea, and vague indigestion during some part of their illness, persistent symptoms referable to the gastrointestinal tract were recorded in only 47 patients. In 25 of these patients there were gross leukaemic lesions in the gastrointestinal tract, in 20 there were associated non-specific lesions in the gastrointestinal tract, and in two patients no obvious abnormality of the gastrointestinal tract could be found. Two patients had palliative surgical operations for intestinal obstruction and gastric ulceration respectively. Fourteen patients with gross leukaemic lesions in the gastrointestinal tract had minimal symptoms, the lesions being incidental findings at necropsy.

HAEMORRHAGE Massive haemorrhage into the gastrointestinal tract occurred in 36 patients, causing 20 deaths. Slight haemorrhage into the gastrointestinal tract occurred in a further 24 patients. The principal data concerning the 36 patients with massive haemorrhage are summarized in Table III. Four patients had haematemesis, 13 had haematemesis and melaena, and 12 had melaena. Necropsies on seven patients who had neither haematemesis nor melaena unexpectedly revealed massive haemorrhages into the gastrointestinal tract. Eleven patients had no obvious macroscopic lesion in the gastrointestinal tract to account for the haemorrhage, but most of these patients were known to have low platelet counts and the cause of

TABLE III

CAUSES OF MASSIVE GASTROINTESTINAL HAEMORRHAGE IN VARIOUS TYPES OF LEUKAEMIA

Type of Leukaemia	No. of Patients	Patients with Massive Haemorrhage	Deaths Due to Haemorrhage	Causes					
				Leukaemic Ulcers	Peptic Ulcers	Gastric Erosion	Non-specific Ulcer	Other Cause	No Obvious Cause
Acute myeloid	54	7	4	0	1	3	0	0	3
Acute lymphatic	48	13	8	2	0	4	3	0	4
Stem cell	13	2	1	1	0	1	0	0	0
Monocytic	33	5	3	3	0	0	2	0	0
Chronic myeloid	56	5	1	0	2	1	0	0	2
Chronic lymphatic	58	3	2	1	0	0	0	0	2
Plasma cell	2	1	1	0	0	0	0	1	0
Total	264	36	20	7	3	9	5	1	11

the bleeding was presumed to be due to the thrombocytopaenia. One patient with plasma cell leukaemia had massive haemorrhage from a carcinoma in the ascending colon (Cornes, Jones, and Fisher, 1961b).

CAUSE OF DEATH Twenty deaths were due to massive haemorrhage into the gastrointestinal tract. Two deaths were due to peritonitis: one from perforation of the caecum by a plaque of monocytic leukaemia, and one from perforation of the transverse colon by chronic lymphatic leukaemia.

DISCUSSION

INCIDENCE At the start of these investigations we expected to find only a few patients with gross leukaemic lesions in the gastrointestinal tract. Wintrobe (1956) and Hayhoe (1960) had drawn our attention to the supposed rarity of these lesions in acute leukaemia, and Forkner (1938), Wintrobe (1956), Debray and Sarakinos (1958), Hayhoe (1960), and others to the supposed rarity of these lesions in myeloid leukaemia. However, in the present study the incidence in acute leukaemia was 18.4%, and in myeloid leukaemia 10.9%. Bearing in mind the retrospective nature of this study we believe that even higher figures would be obtained in a planned, forward-looking study from a centre specializing in the treatment of these disorders.

GASTRIC LESIONS Dameshek and Gunz (1958) draw attention to the stomach as the commonest part of the gastrointestinal tract to be affected by leukaemia. In the present study the incidence of gross leukaemic lesions in the stomach was 5.7%. The reported incidence of these lesions varies from 3.9% (Ikeda, 1931) to 10.9% (Wahl and Hill, 1956).

The commonest type of lesion found is a slightly raised, plaque-like thickening of the stomach wall, usually associated with overlying mucosal ulceration. These lesions may give some difficulty in clinical diagnosis. One patient presenting with a gastric

ulcer was diagnosed clinically as a case of peptic ulceration, and an operation was performed. Examination of the operation specimen and subsequent blood studies, however, established the diagnosis of a previously unsuspected chronic lymphatic leukaemia. Cavins, Levin, and Day (1959) describe a similar case in a patient with chronic myeloid leukaemia, the initial diagnosis being carcinoma of the stomach. Steinbrinck (1938) describes two patients with leukaemic infiltration of the stomach wall diagnosed radiologically as gastric carcinoma.

Although the raised nodular lesions found in the present study were small and multiple, large nodules have been reported in acute myeloid leukaemia (Kahn, 1912), subacute lymphatic leukaemia (Wahl and Hill, 1956), and chronic lymphatic leukaemia (Koster and Blickman, 1958).

Diffuse infiltrations producing a convoluted, brain-like appearance of the gastric mucosa have been reported in acute myeloid leukaemia (Cattan, Frumusan, Bensaude, Breynaert, Israel, and Habib, 1953), acute lymphatic leukaemia (Jørgensen, 1935; Touw and Graafland, 1939; Wahl and Hill, 1956), acute monocytic leukaemia, stem cell leukaemia (Wahl and Hill, 1956), and chronic lymphatic leukaemia (Boikan, 1931; Lüdin, 1933; de Jongh, 1934; Pearson *et al.*, 1943; Nagel, 1952; Stobbe, 1958; and others). Similar lesions have been reported in lymphosarcoma and Hodgkin's disease.

INTESTINAL LESIONS Plaque-like thickenings, raised nodular lesions, diffuse infiltrations, and leukaemic polyposis are the four types of lesion seen in the small and large intestine, and it is possible to find more than one type occurring in the same patient.

Taken together leukaemic plaques and raised nodules account for most of the lesions seen. To a certain extent they represent enlargement and leukaemic replacement of the solitary and aggregated lymphatic nodules found normally in the small and large intestine. However, these nodules are usually

indistinct in middle age, and absent from the elderly, and in many patients the leukaemic lesions and the Peyer's patches are quite separate (Virchow, 1856; Müllern and Grossmann, 1912; Köhn, 1951; and others). Moreover the leukaemic lesions can be of considerable size. Askanazy (1894) describes a 10 cm. plaque of acute myeloid leukaemia in the terminal ileum. Campbell, Henderson, and Croom (1936) describe an 8 cm. plaque of monocytic leukaemia in the lower third of the rectum. Blatt and Chapman (1960) describe colonic lesions in acute myeloid and chronic lymphatic leukaemia measuring 10 and 15 cm. respectively.

Many of the early reports describing leukaemic plaques or raised nodular lesions refer to cases of myeloid leukaemia (Askanazy, 1894; Dennig, 1900; Schultze, 1906; Kahn, 1912; Müllern and Grossmann, 1912; Herxheimer, 1913; and others). Ulcerated plaques may be covered by a greyish membrane and simulate diphtheritic ulceration or pseudo-membranous colitis (Obrastzow, 1890). Occasionally ulcerated plaques in the small intestine of patients with acute leukaemia simulate typhoid, and the associated fever, prostration, and colicky abdominal pain lead to difficulties in diagnosis (Virchow, 1856; Warthin, 1904; Herxheimer, 1913; Klostermeyer, 1934; Köhn, 1951; and others). Because leukaemic plaques involve the muscle coats more frequently than the raised nodular lesions they are more likely to be associated with intestinal perforation. Intestinal perforation with death from peritonitis has been reported in acute leukaemias (Cooke, 1933; Leach, 1961), myeloid leukaemia (Jones, 1940; Dameshek and Gunz, 1958), monocytic leukaemia, and chronic lymphatic leukaemia. Nodular lesions, on the other hand, are more likely to cause intussusception and death from intestinal obstruction (Kramer, 1934; Stobbe, 1958).

Diffuse leukaemic infiltrations producing a convoluted brain-like appearance of the intestinal mucosa have been seen in the duodenum (Nagel, 1952; Boquien, Kernéis, and Guénel, 1958), colon (Jørgensen, 1935; Pearson *et al.*, 1943), and recto-sigmoid (Girard, Fraisse, Noël, and Grivet, 1955). They appear to be less common than similar lesions in the stomach.

Several patients with multiple intestinal polyps of leukaemic origin have been reported in the literature. In the majority of cases the entire intestinal tract is affected, but occasionally the polyps are confined to the small intestine (Letulle and Halbron, 1905; Jørgensen, 1935), or to the large intestine (Nagel, 1952). These polyps have been seen in acute myeloid leukaemia (Blatt and Chapman, 1960), acute lymphatic leukaemia (Jørgensen, 1935), stem cell leukaemia (Comolli, 1949), chronic myeloid leuk-

aemia (Letulle and Halbron, 1905), and chronic lymphatic leukaemia (Boikan, 1931; Mead, 1933; de Jongh, 1934; Nagel, 1952; Blatt and Chapman, 1960).

RECTAL LESIONS Only seven patients in the present study had gross leukaemic lesions in the rectum, and in six the lesions were small, multiple, non-ulcerated, and apparently without clinical significance. In three patients the rectum was the only part of the gastrointestinal tract affected, a feature noted by others (Layani, Aschkenasy, and Sicot, 1947; Girard *et al.*, 1955).

Most of the recorded cases occurred in acute leukaemias, and the lesions were large and ulcerated (Vachon, Lehmann, Pellet, and Delahaye, 1956; Picard, Hardy, and Meillet, 1957). Occasionally patients presented with these lesions and an initial diagnosis of carcinoma was made (de Jongh, 1934; Haining, Kimball, and Janes, 1935; Layani *et al.*, 1947; Levrat, Richard, Normand, and Anjou, 1955).

PEPTIC ULCERS Although there does not appear to be any significant association between peptic ulceration and leukaemia (Niwayama and Terplan, 1959; Tokoro, 1958), the incidence of peptic ulcer appears to be higher in myeloid than in other types of leukaemia (Wintrobe, 1956; Hayhoe, 1960; Cornes, Jones, and Fisher, 1961a). A relationship between peptic ulceration and proliferative disorders of the bone marrow is suggested by the high incidence of peptic ulcer in myeloid leukaemia, polycythaemia (Wilbur and Ochsner, 1935; Lawrence, 1955; and others), monocytic leukaemia, and multiple myeloma (Cornes *et al.*, 1961a). Peptic ulceration may sometimes draw attention to a previously unsuspected leukaemia (Blackburn and Daniel, 1957), and occasionally the distinction between peptic ulcer and true leukaemic ulceration is extremely difficult (Conley and Wilson, 1950). Sometimes peptic ulcers dominate the patients' illness, and may cause death from haemorrhage or peritonitis.

ANAL LESIONS Considering the frequency of oropharyngeal lesions in patients with leukaemia it is surprising how few anorectal lesions have been reported in the literature. Marks (1953) and Vachon, Lehmann, Pellet, and Delahaye (1956) describe patients with combined oropharyngeal and anorectal lesions. Anal ulceration is sometimes the earliest clinical manifestation of an acute leukaemia (Blank, 1955; Vogel, 1960). The cause of this ulceration is uncertain. In some cases it appears to be associated with thrombosis and sloughing of haemorrhoids (Walsh and Stickley, 1934; Blank, 1955; Horowitch and Wasserman, 1959), and in others with actual

ulceration by leukaemic tissue (Cattan *et al.*, 1953; Birnbaum and Ahlquist, 1955; Bluefarb, 1957).

CLINICAL FEATURES In our experience persistent symptoms referable to the stomach and intestines are usually associated with gross lesions in those organs. However, as our study shows, a considerable number of patients with these lesions have no specific symptoms whatever. We have already drawn attention to patients with unsuspected leukaemia presenting with ulcerating lesions in the gastrointestinal tract. These may be diagnosed as peptic ulcer, gastric carcinoma, typhoid, ulcerative colitis, and rectal carcinoma. The importance of these lesions lies in the distressing and persistent symptoms which they can produce, by the occasional difficulties in diagnosis, and by deaths from intestinal obstruction, haemorrhage, and peritonitis.

Although leukaemic ulceration is an important cause of massive haemorrhage into the gastrointestinal tract the majority of cases are due to gastric erosions, non-specific ulceration, and thrombocytopenic purpura (Leach, 1961). Palliative operations for massive haemorrhage into the stomach (Palmer, 1955) or intestines (Wolma and Lynch, 1959) have occasionally eased much suffering and prolonged the patient's life. The importance of a post-mortem examination of the gastrointestinal tract was demonstrated in our study of seven patients who had neither haematemesis nor melaena. Necropsies unexpectedly revealed massive haemorrhage into the gastrointestinal tract as the cause of death in every case.

CONCLUSIONS

We hope that this study and our rather cursory survey of cases reported in the literature will draw attention to the importance of leukaemic lesions in the gastrointestinal tract. These lesions are more common than is generally supposed, and in some patients they are the most important feature of their illness. Finally we would urge a careful examination of the gastrointestinal tract and anal canal in all patients with leukaemia, and make a plea that representative sections be taken for histology from all the lesions found.

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