Malabsorption in relation to abdominal irradiation and quadruple chemotherapy for lymphosarcoma

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Summary

A case of severe diarrhoea and steatorrhoea following chemotherapy and abdominal irradiation for lymphosarcoma, is described. Investigations demonstrated bile acid malabsorption, and treatment with cholestyramine and a low fat diet was successful.

A questionnaire was sent to thirty-two subjects who had undergone similar treatment for similar pathology and failed to demonstrate any sustained alteration of bowel function. Additionally, nine of these subjects underwent a ^{14}C -glycocholic acid test and no evidence of interruption of the enterohepatic circulation of bile acids was found.

Introduction

Gastrointestinal side effects of abdominal irradiation can be severe (Sobo and Johnstone, 1973). Acute manifestations include nausea, vomiting and diarrhoea, while chronic effects may result in intestinal fistula formation, strictures, endarteritis and lymphatic obstruction (Brown, 1962; Halls, 1965; Wiernik, 1966). Malabsorption may follow any of these complications and is well recognized after pelvic irradiation (Tankel, Clark and Lee, 1965). It has only occasionally been documented after abdominal irradiation with or without chemotherapy (Duncan and Leonard, 1965).

A patient with severe persistent diarrhoea and steatorrhoea following a single course of abdominal irradiation in addition to regular cytotoxic chemotherapy for lymphosarcoma was recently investigated. He was found to have bile acid malabsorption and responded to treatment with a bile acid sequestering agent. Subsequently, bowel function in a series of similarly treated patients was investigated and the ^{14}C -glycocholic acid (^{14}C -GCA) test (Fromm and Hofmann, 1971) was used in a number of these subjects to seek evidence of any similar interruption of the enterohepatic circulation.

Case report

A 58-year-old man was seen in March 1973 with a 3-month history of exertional dyspnoea, nocturnal sweating and slight weight-loss. Examination revealed a partial right-sided pleural effusion. Investigation included a thoracotomy when he was shown

to have a lymphosarcoma (stage IV) with extensive infiltration of lung tissue and pleura with metastatic spread to involve mediastinal and para-aortic lymph nodes. There was no history of any gastrointestinal symptoms and a γ -scan of liver and spleen was negative.

He was commenced on quadruple chemotherapy (nitrogen mustard, 7.5 mg; vincristine, 2.0 mg i.v.—days 1 and 8; procarbazine, 50 mg b.d.; and prednisolone, 10 mg t.i.d. orally for 2 weeks) on a monthly regime. After three courses of chemotherapy he was given one course of mantle and inverted 'Y' irradiation (total nodal) and received 800 rad to the abdomen. During radiotherapy he complained of watery diarrhoea which cleared spontaneously within a few days.

He remained well, in clinical remission, until January 1974 when he required emergency admission for acute abdominal pain. All investigations which included a laparotomy were negative and he made a spontaneous improvement. Subsequently he complained of persistent, offensive, watery diarrhoea. This persisted over the next 6 months and remained resistant to a variety of anti-diarrhoeal agents including codeine phosphate, diphenoxylate hydrochloride and methyl cellulose. He was therefore admitted for further investigation. This may be summarized as follows:

Haematology. Hb 12.2 g/dl; WBC $5.0 \times 10^7/\text{l}$ (lymphocytes = 21%), ESR (Westergren) 12 mm/hr. Folate 5.4 ng/ml; B12 240 pg/ml.

Biochemistry. Calcium 2.30 $\mu\text{mol/l}$; phosphate 1.36 $\mu\text{mol/l}$; protein 2 g/l; albumin 35 g/l; alkaline phosphatase 24 KAU; SGOT 54 mi.u./ml; IgG 10.4 g/l; IgA 1.0 g/l; IgM 0.5 g/l.

Gastrointestinal (GI)

Structure. Upper GI endoscopy, sigmoidoscopy, full barium series, jejunal and rectal histology—all normal.

Function. Faecal volume averaged 409 g/day; faecal fat (100 g intake) averaged 57 mmol/day (normal <21); Schilling test (with intrinsic factor) = 16.5% in 24 hr (normal >8%); Lundh test (Wiggins, 1967)—trypsin 17.3 $\mu\text{mol H}^+ \text{ml}^{-1}$ (normal >8); ^{51}Cr -albumin loss in faeces 0.9% in 5 days (normal <1%); faecal bile acids (Sheltawy and Losowsky,

TABLE 1. Results of ^{14}C -glycocholic acid test

Study	Symptoms	*Breath $^{14}\text{CO}_2$ (%)	24-hr faecal weight (g)	*Faecal ^{14}C	Drug therapy
1	Steatorrhoea	8.4	490	Not analysed	Nil
2	Steatorrhoea	1.6	690	15%	Metronidazole 200 mg t.i.d.
3	Normal, formed stools	13.8	25	—	Cholestyramine 4 g t.i.d.

* Following ingestion of 5 μCi of ^{14}C -glycocholic acid, cumulative excretion of ^{14}C was measured in breath samples for 6 hr and in faeces for 24 hr: our normal range is breath output <4.0% and faecal output <7.0%.

TABLE 2. Results of studies (see text)

Case no.	Diagnosis	Treatment chemo-therapy/radiotherapy	Diarrhoea	*Breath ^{14}C (%)	*Faecal ^{14}C (%)	24-hr faecal weight (g)
1	Hodgkin's (IVB)	M.O.P.P.	—	1.4	—	0
2	Hodgkin's (IIB)	2,200 rad	—	2.0	11.9	245
3	Hodgkin's (IVA)	M.O.P.P.	—	0.5	9.5	160
4	Giant cell follicular lymphoma	3,500 rad	—	1.3	4.2	130
5	Lymphosarcoma (IVB)	C.O.A.P. + 3,500 rad	—	4.0	—	0
6	Hodgkin's (IIA)	3,500 rad	—	0.4	—	50
7	Reticulum cell sarcoma	C.O.A.P. + 3,500 rad	—	0.4	—	50
8	Hodgkin's (IIIA)	2,290 rad	—	0.3	—	50
9	Hodgkin's (IIB)	3,500 rad	—	2.4	9.2	130

M.O.P.P. = mustine, vincristine, procarbazine, prednisolone; C.O.A.P. = cyclophosphamide, vincristine, doxorubicin, prednisolone.

* See legend to Table 1.

1975) 3477 and 2578 $\mu\text{mol}/24$ hr on two occasions (normal <880). Thin layer chromatography small bowel aspirate (Hofmann, 1962) revealed trace of unconjugated bile salts. ^{14}C -glycocholate test (see Table 1).

Bacteriology. Stool cultures negative, jejunal contents and mucosa negative for *Giardia*.

In view of the evidence of fat malabsorption he was commenced on a low fat diet. His symptoms improved with decreased bowel frequency although his faeces remained non-formed.

The initial ^{14}C -GCA test (Table 1) indicated excessive bile acid deconjugation. The finding of trace amounts of unconjugated bile acids on thin layer chromatography suggested that this was due to small bowel bacterial overgrowth. He was therefore given a trial of an oral antibiotic and breath $^{14}\text{CO}_2$ output became normal although his symptoms remained unchanged (Table 1). Faecal ^{14}C output was found to be increased suggesting bile acid malabsorption and in addition the total 24-hr faecal bile acid output was markedly raised. He was therefore given a trial of cholestyramine (4 g t.i.d.), a bile acid sequestering agent, and improved markedly with restoration of a normal bowel action.

Comments and further course

He remains well 2.5 years after the onset of diarrhoea with no clinical or laboratory evidence of

recurrence of his lymphosarcoma. His bowel habit is readily controlled by cholestyramine and restriction of fat intake. His chemotherapy continues. Current biochemistry (including the previously raised alkaline phosphatase and SGOT) is normal.

Further studies

Thirty-two patients who had received either abdominal irradiation (total nodal) or regular cytotoxic chemotherapy (or a combination of both) for Hodgkin's disease or lymphoma were studied. All were judged to be in clinical remission. Each was asked to complete a simple questionnaire describing changes (if any) experienced in bowel function during initial treatment and also while in subsequent remission. Nine of these patients agreed to undergo a ^{14}C -GCA test performed in a standard manner (Fromm and Hofmann, 1971).

Of the patients studied thirteen were receiving regular cytotoxic chemotherapy, seventeen had been treated with total nodal irradiation alone (2000–3500 rad) and two received a combination of treatment. While undergoing initial chemotherapy, five patients recorded a change in bowel habit with the passage of frequent loose stools. However, in all cases bowel habit returned to normal within a few days without treatment. While on maintenance chemotherapy only one subject complained of occasional loose stools with four or five bowel actions

per day. Three patients who received radiotherapy had initial diarrhoea which required small amounts of codeine phosphate for control; subsequently none of this group described any increase in bowel frequency. Neither of the patients who were treated with a combination of therapy reported any alteration of bowel habit.

The results of the ^{14}C -GCA tests performed in nine of these subjects are shown in Table 2. All results are within the normal range apart from a marginally elevated faecal ^{14}C output in case 2 in whom bowel function was quite normal.

Discussion

Malabsorption following abdominal irradiation is rare and reports of such cases have usually followed pelvic irradiation (Tankel *et al.*, 1965). Radiation injury may cause malabsorption via several different mechanisms. These include formation of intestinal fistulae, mucosal damage, mesenteric ischaemia and lymphangiectasia. The disordered physiology can include interruption of the enterohepatic circulation of the bile salts, either from the creation of a stagnant-loop syndrome or from terminal ileal damage (Fromm, 1973). Where the faecal ^{14}C output is measured, the ^{14}C -GCA test may be used to distinguish these conditions (Fromm and Hofmann, 1971).

Newman and his colleagues (Newman *et al.*, 1973) have studied bowel function in women following pelvic radiotherapy. They found that a majority reported a permanent change in bowel habit with increased bowel frequency and that the ^{14}C -GCA breath test was abnormal in sixteen of seventeen subjects. However, they did not measure faecal ^{14}C output.

From the series reported here, it would appear that a permanent alteration of bowel function is an uncommon sequel of either serial cytotoxic chemotherapy or abdominal radiotherapy. No evidence of interruption of the entero-hepatic circulation was found using the ^{14}C -GCA test in nine subjects. Presumably the amount of radiation damage caused to the small bowel during total nodal abdominal irradiation via the linear accelerator is less than in the case of pelvic radiotherapy when treatment may consist of intra-cavity radium and where the total dose is concentrated on a smaller area.

In the case described there is clinical evidence of impaired fat and water absorption. The high faecal ^{14}C output together with the high total faecal bile acid output indicates bile acid malabsorption. This is supported by the good clinical response to cholestyramine therapy but the reason for the bile acid malabsorption is unclear. If the underlying disease were still active and involving the intestinal mucosa, then malabsorption could result. However, the patient remains in good health more than 3 years

after original presentation without evidence of recurrent disease and a laparotomy at the start of his gastrointestinal symptoms was negative. Other mechanisms of diarrhoea and steatorrhoea have been assessed. Altered immunity might predispose to bacterial overgrowth of the small bowel or giardiasis but serum immunoglobulin levels were normal, giardiasis was excluded and there was no response to metronidazole. Severe pancreatic damage is excluded by the normal pancreatic function studies. Lymphatic obstruction is unlikely because the small intestinal biopsy showed no lymphatic dilatation, faecal loss of ^{51}Cr was normal, as were serum immunoglobulins and peripheral lymphocyte count. Bile acid malabsorption suggests ileal mucosal damage but it is noteworthy that the radiology of the ileum and the Schilling test were normal.

In conclusion, this patient appears to have an isolated malabsorption of bile acids attributable to treatment of his lymphosarcoma. This complication is probably very unusual and has not been reported before.

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