Afr. J. Med. med. Sci. (1976) **5**, 185–190.

A critical evaluation of the carcinogenic role of amoebiasis with special reference to a case of double primary malignancies

A. A. ABIOYE

Department of Pathology, University of Ibadan, Medical School, University College Hospital, Ibadan, Nigeria

Summary

The case of a 45 year old man with double primary malignancies of unrelated organs—namely, amoebiasis-associated colo-rectal and renal cell carcinomas, is reported. The problem of carcinogenic role of amoebiasis in particular and that of parasitic diseases in general, is discussed and the literature briefly reviewed.

Résumé

Le cas d'un homme age de 45 ans atteint d'une double malignite primaire de deux organes sans relation est decrite ici: il s'agit d'une amibiase et d'un carcinome des cellules renales et colo-rectales.

Nous etudions le probleme du role des amibiases dans le developpement de carcinomes en particulier, et le probleme des maladies parasitaires en general, et la litterature existant a ce sujet est rapidement passee en revue.

Introduction

Interest in the possibility that human amoebiasis may be associated with colo-rectal carcinoma has been stimulated by several authors (Harris 1898; McDonal 1965 and Trevene Mere, 1967). The most common amoebic infection is proctocolitis. Amoebic proctocolitis with or without ulceration was found in 80·7% of a large series of cases of amoebiasis reported from the University College Hospital, Ibadan. (Abioye & Edington 1972). The disease has very serious complications and/or sequelae, especially when not properly diagnosed and treated. Amoebic granuloma or amoeboma of the colon and rectum also occurs. This was found in the caecum in 85% of cases reported by Trevine Mere (1967) and in 45% of those studied in the United States by Spicknal & Peirce (1954). The latter workers also found the lesion in the rectum in 14% of cases.

Correspondence: Dr A. A. Abioye, Department of Pathology, University College Hospital, Ibadan, Nigeria.

Fortunately, malignancies of the colon and rectum are very rare among Nigerians. Studies by Williams & Edington (1967) yield an incidence of about 3% of all malignancies in the University College Hospital, Ibadan. Of the large bowel cancers which do occur, 45·8% are in the rectum while 54·2% occur in the colon. Of the colonic cancers, 37·4% are in the caecum; 12·1% in the ascending colon including the hepatic flexure; 7·2% in the transverse colon; 6·0% in the descending colon and splenic flexure whilst 26·5% occurred in the sigmoid colon.

In the University College Hospital, Ibadan, we became interested in the overall carcinogenic role of human parasitosis in general, work is in progress to assess such possible role. However, in the course of the study a patient with double primary malignancies, namely, amoebiasis-associated colo-rectal carcinoma and clear cell carcinoma of the kidney came to autopsy. The case is considered to have stimulated sufficient interest to warrant its documentation as the first case of amoebiasis-associated double primary malignancies in a Nigerian.

Case Report

A 45-year old man (O.S.) was admitted to the hospital with a 6 month history of recurrent episodes of mucoid bloody diarrhoea, poor appetite, back and chest pain and occasional dizziness. Physical examination revealed left hypochondrial tenderness and a fleshy annular growth in the rectum, 5cm from the anal verge. The stool was positive for occult blood. A provisional diagnosis of carcinoma of the rectum

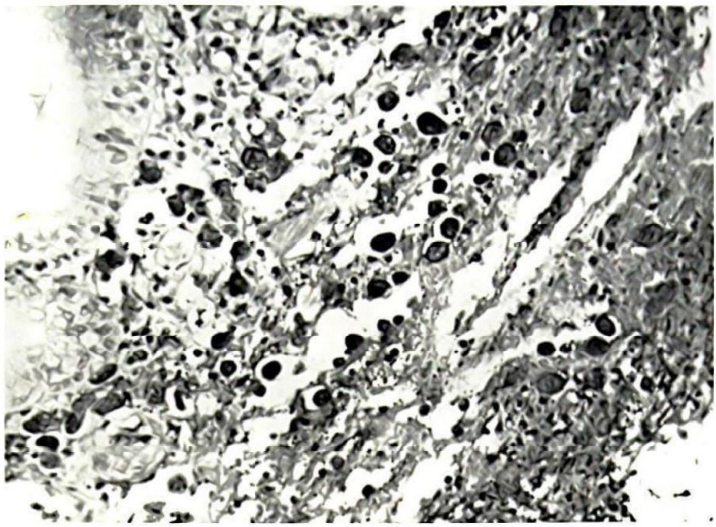

FIG. 1. Numerous trophozoites of *E. histolytica* in necrotic tissue surrounded by clear haloes. H. & E. ×210.

was made, but investigations to exclude a more benign condition such as amoebiasis, were also undertaken. All specimens of stool were negative for amoebic trophozoites until 3 weeks after hospitalization, when trophozoites of *Entamoeba histolytica* with intracellular red blood cells were identified. This correlated with rectal biopsy histological finding (Fig. 1), confirmed the diagnosis of amoebic proctocolitis.

After six weeks of hospitalization the patient developed gross ascites and physical examination at this stage revealed a nodular tender enlarged liver. The patient died 5 days later before a full work-up for the possibility of primary tumour was completed.

Autopsy findings

The main abnormalities on opening the body included ascites with about a quarter of a litre of clear straw-coloured fluid. There were a few multiple firm tumour nodules measuring from 0·5 to 4 cm diameter on the cut surface of the grossly congested lungs. The liver was grossly enlarged and weighed 4·44 kg with numerous yellowish white umbilicated tumour nodules measuring from 1·0 to 5·0 cm in diameter. The cut surface of the liver revealed approximately 50% of it to consist of scattered tumour nodules (Fig. 2). The intervening liver tissue showed the normal lobular architecture. The larger tumour nodules had necrotic centres and were all bulging on cut surface.

The intestines were unremarkable except for the rectum. At approximately 7 cm from the anal sphincter, there was a roughened, fungating necrotic annular constricting tumour measuring 8 cm in length (Fig. 3). Over the left parietal cortex was a 2 cm diameter firm yellowish tumour and over the right frontal cortex was a 3 cm diameter similar yellow tumour.

With these findings in a middle-aged man having a previous history of recurrent bloody diarrhoea, psychotic symptoms, rectal mass, tumour secondaries in the lungs, coupled with an ante-mortem histologic diagnosis of rectal amoebiasis, a provisional anatomical summary of carcinoma of rectum with metastases to the liver, lungs, bladder wall, brain, and left kidney with super-imposed amoebic proctocolitis was made.

Histology

The only rectal biopsy performed during life showed extensive protocolitis with numerous trophozoites of *E. histolytica* in the mucosa (Fig. 1). The

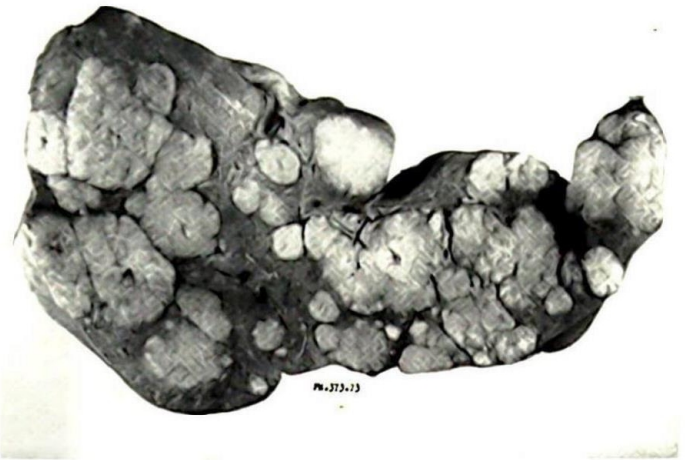

FIG. 2. Section of the liver showing scattered metastatic nodules.

FIG. 3. Section of the rectum showing necrotic annular constricting tumour.

post-mortem histology showed marked congestion and haemorrhages surrounding varying size metastatic tumour nodules composed of well-differentiated mucin secreting adenocarcinoma in some areas and an apparently similar picture dominated by areas of necrosis in other parts. The sections of the liver show disruption of the lobular architecture by haemorrhage and multiple large and small metastatic deposits of mucin secreting adenocarcinoma similar to those in some parts of the lung. The section of colon shows grossly thickened mucosa replaced by anaplastic mucin producing glands which infiltrated the muscle coat and extended to the serosal surface. In many areas the tumour appeared necrotic but no amoebae were seen.

The section of the left kidney shows multicystic nodules with intervening solid areas composed of clear cells growing in a solid alveolar pattern (Fig. 4).

A final histological diagnosis of amoebiasis with associated carcinoma of the rectum and clear-cell carcinoma of the kidney was returned.

Discussion

Over the years cases of multiple malignancies have been reported from clinical and necropsy material by various authors (Warren & Gates, 1932; Warren & Ehrenreich, 1944; Bacon, 1945; Slaughter, 1946; and Dibble & Chambers, 1960), and a study of these cases shows that they fall into four groups. In the great majority two or more primary tumours have appeared in the same organ, such as the large bowel, the skin or the mouth. Occasionally, multiple tumours have occurred in paired viscera or in viscera of the

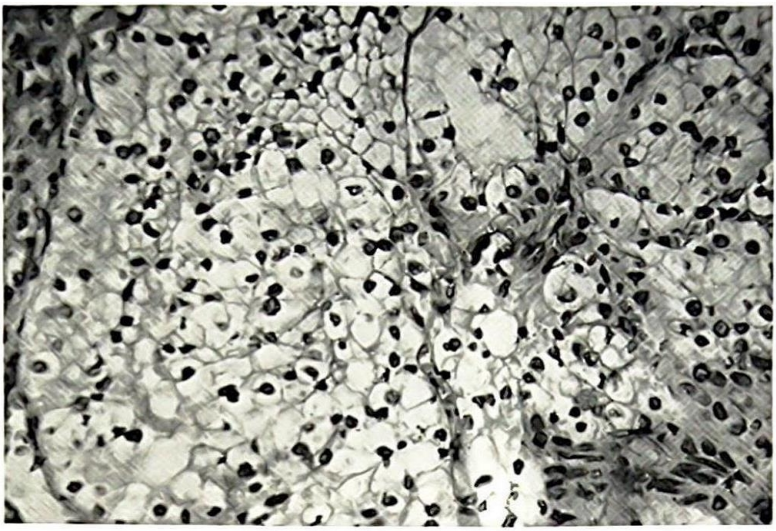

FIG. 4. Histologic section of clear cell carcinoma of the kidney. H. & E. ×145.

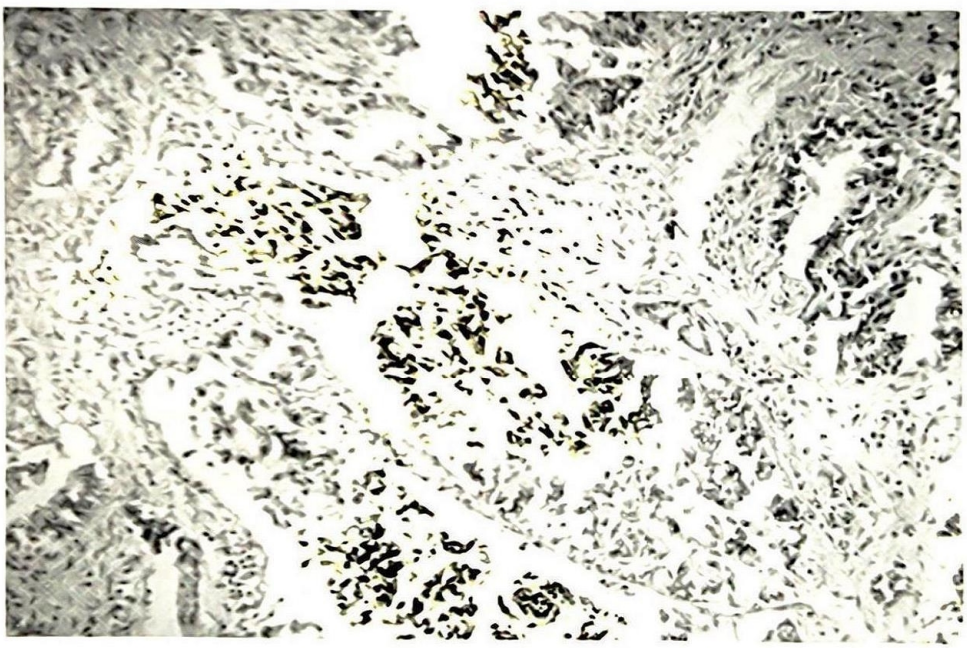

FIG. 5. Histologic appearance of well differentiated adenocarcinoma. H. & E. ×114.

same system—for example, the renal pelvis and ureter—finally to a lesser extent multiple primary malignant tumours have occurred in unrelated organs, as in the case reported here.

In a comprehensive review of the literature Warren & Gates (1932), collected thirty-seven cases which had been reported with three malignant tumours, but the only reference to a patient with two primary carcinomata of the large bowel and a primary carcinoma of the breast was that of Lane (1909). Since then, there have been other isolated reports of multiple carcinomata including those of Warren & Ehrenreich (1944) and Cahan (1955). The presence of multiple primary malignant tumours in the patient poses a problem. Is one of the tumours a metastasis of the other? In this case the clinical presentation (when viewed in retrospect) was very much suggestive of genito-urinary disease overshadowed by symptoms of gastro-intestinal tract disease. In addition, the histological appearances of the tumours of the recto-sigmoid and the kidney together with those of the metastases in the lungs were quite different and there was nothing to support a suggestion that one of the tumours was the primary growth and the others were metastases.

Usually, multiple diagnoses are to be avoided if all the lesions may be covered by a single diagnosis, but the possibility of a single diagnosis does not pertain here. The rectal well-differentiated adenocarcinoma would not have produced metastases in the lungs and brain, composed of clear cells growing in a solid alveolar pattern with areas of haemorrhage and necrosis, features more likely to be those of clear cell carcinoma of the kidney. Furthermore, it is very unlikely that a clear cell carcinoma of the kidney would have given rise to recurrent episodes of mucoid diarrhoea as occurred in this patient, especially when histological appearances of the tumours were later found to be quite distinct. It can be argued that the gastro-intestinal symptoms in this patient were purely those of the super-imposed amoebiasis; this latter condition created the apparent difficulty both in the diagnosis and subsequent management of the patient.

In spite of the fact that a figure as high as 15% has often been quoted for amoebiasis-associated colo-rectal malignancy (Camacho, 1971); a review of the literature has not revealed any report of a case associated with multiple primary malignant tumours. The association of amoebiasis with internal malignancy is now well established. Since this was first noted by Harris (1898), there have been many subsequent reports to confirm the association. There is diversity of opinion as to whether the relationship is merely coincidental or that amoebiasis may predispose to development of cancers. Thus while Edington (1965) and Williams & Edington (1967) contend that the intermittent infections and infestations, such as amoebic and bacillary enterocolitis, or schistosomiasis, do not predispose to development of rectal carcinoma and considered the finding fortuitous, Camacho (1971), firmly believed that amoebic granuloma may be precancerous, and in cases where amoebic granuloma co-existed with malignancy, he believed that the granuloma grows and regresses until, finally the malignancy imposes itself.

While one cannot categorically dispute either of these views at this stage, a closer study of the recorded cases reveals well-defined facets of this association. First, in this connection it is interesting to note that of the twelve cases of squamous cell carcinoma of colon and rectum studied by Williams & Edington (1967), eleven occurred in the anal canal whilst the only extra-anal one was found in the caecum associated with ova of *S. mansoni*. Secondly, when one considers the general distribution of malignant tumours of large intestine and rectum, as studied by Williams & Edington (1967) in Ibadan and compares this with the general distribution of amoebic lesions of the gastro-intestinal tract, one cannot but make some inferences as to their similarity and perhaps be tempted to draw some conclusions. According to Williams & Edington (1967), the frequency of malignancy diminished progressively with the distance from the ileo-caecal valve until the sigmoid flexure was reached.

Although these authors did not discuss the possible mechanism for such a distribution, it again happens to coincide with the distribution of amoebic lesions in the gut (Faust, 1943 and Abioye, 1971). The explanation for the latter being based on suggested mechanism that the preponderance of primary amoebic lesions in the caecal area may be due to the fact that this is the first level of the bowel where any appreciable amount of intestinal stasis occurs. This also explains the apparent rarity of amoebic lesions in the small intestines—an event which may be made possible by the regurgitation of the trophozoites into the posterior segment of the ileum and thus allows the tissue invasion of this part of the intestine.

By a somewhat similar mechanism one may be tempted to explain the rarity of malignancies in the

small intestines. The average length of the small intestine is 7m, the upper two-fifths being jejunum and the lower three-fifths the ileum. The fact that on such a long stretch of viscus only a small proportion of malignancies occurs remains a puzzle. Several theories have been postulated to explain this low incidence. All seem to agree that the lack of stasis, the absence of abrupt angulations, the fluidity of the contents and its alkaline pH may play a role. By this argument an analogy can be made between the distribution of large bowel cancers and amoebic lesions, and attempt to explain the co-existence of the two conditions on these common grounds.

It may still be possible to explain the association of amoebiasis and colo-rectal carcinoma as a superimposition of amoebiasis on malignancy due to the lowering of patient's resistance and gives rise to a process similar to the anergy which often accompanies malignant lymphomas; rendering the colonic mucosa susceptible to amoebic infections. This may be the situation in this case because it was not until 3 weeks after hospital admission could amoebae be isolated from the patient's stool, in spite of repeated examinations. It is still possible that malignancy and parasitosis operate synergistically to give enhanced pathogenicity by a complex mechanism which is yet certainly poorly understood. One can only try to strike a compromise between the conflicting views and suggest that the carcinogenic role of amoebiasis and of any other hitherto suspected parasitic disease be subjected to a more stringent clinical, as well as, experimental studies with a view to clarifying the significance of amoebiasis and malignancy.

The possible significance of amoebiasis in the aetiogenesis of renal carcinoma is still more intriguing and difficult to explain. However, there has been considerable discussion in the literature on the occurrence of multiple tumours compared with that of single ones. Opinions vary greatly on this issue and widely differing conclusions based on clinical, experimental, pathological, or necropsy material have been suggested by most authors. This problem will not be further complicated by apportioning a role to amoebiasis on the basis of this single case. It is hoped by drawing attention to the possibility of this rare association, clinicians working in areas where parasitosis may be super-imposed on malignancy may suspect a combining of factors.

In conclusion multiple primary malignant tumours of the colon and unrelated organs are very rare. Primary tumours are usually solitary and multiple carcinomas associated with amoebiasis are extremely rare. Opinions of authorities differ concerning the carcinogenic role of parasitosis. It seems impossible to predict which patients will have such associated condition and which will not. More controlled studies should be undertaken to provide an estimate of the percentage of patients with parasite associated malignancy.

References

ABIOYE, A.A. (1971) *Immunopathology of amoebiasis in Ibadan.* Thesis, University of Ibadan, Ibadan, Nigeria.

ABIOYE, A.A. & EDINGTON, G.M. (1972) Prevalance of amoebiasis at autopsy in Ibadan. *Trans. R. soc. Trop. Med. Hyg.* **66**, 754.

BACON, H.E. (1945) *Anus, Rectum, Sigmoid Colon.* 2nd edn, pp. 560. Lippincott Co. Philadelphia, Pennsylvania, U.S.A.

CAHAN, W.G. (1955) Lung cancer associated with cancer primary in other sites. *Am. J. Surg.* **89**, 494–514.

CAMACHO, E.C. (1971) Amebic granuloma and its relationship to cancer of the caecum. *Dis. Col. Rect.* **14**, 12.

DIBBLE, P.A. & CHAMBERS, R.G. (1960) Multiple primary malignant tumours. *Laryngoscopic* (St Louis) **70**, 1647.

EDINGTON, G.M. (1965) Cancer of the alimentary tract in Africa. *Union Internationale Contre le Cancer*, Symposium Geneva, 1965.

ESTRADE, J. (1955) Deux tumours secondaires sténosantes du grêle. *Bull. Assoc. franc l'etude cancer*, **42**, 498.

FAUST, E.C. (1943) Horizons of American Tropical Medicine —presidential address, American society of Tropical Med. *Am. J. Trop. Med.* **23**, 1–10.

HARRIS, H.F. (1898) Amoebic dysentery. *Am. J. Med. Sci.* **115**, 384.

LANE, W.A. (1909) Quoted by Bacon (1945) *Anus, Rectum & Sigmoid Colon*, 2nd edn pp. 560. Lippincott Co., Philadelphia, Pennsylvania, U.S.A.

MCDONALD, G. & MOORE, M.M. (1965) Primary gastric amebiasis superimposed on reticulum cell sarcoma. *J. Am. med. Ass.* **193**, 971–972.

SLAUGHTER, D.P. (1946) Multicentric origin of intraoral carcinoma. *Surgery*, **20**, 133–146.

SPICKNALL, C.G. & PEIRCE, E.C. (1954) Amebic granuloma–report of four cases and review of the literature. *New Eng. J. Med.* **25**, 1055–1062.

TREVINE MERE, H. (1967) Granuloma amibiano del colon. *Rev. Gastroenterol. Med.* **32**, 443.

WARREN, S. & GATES, O. (1932) Multiple primary malignant tumours—survey of the literature and statistical study. *Am. J. Cancer*, **16**, 1358–1414.

WARREN, S. & EHRENREICH, T. (1944) Multiple primary malignant tumours and susceptibility to cancer. *Cancer Res.* **4**, 554–570.

WILLIAMS, A.O. & EDINGTON, G.M. (1967) Malignant disease of the colon, rectum and anal canal in Ibadan, Western Nigeria. *Dis. Col. Rectum*, **10**, 301–308.

(*Received* 1 *April* 1976)