Malakoplakia of the gastrointestinal tract

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Summary
The clinical and pathological features of 3 cases of colonic malakoplakia are documented thereby bringing to 34 the total of recorded cases of malakoplakia involving the gastrointestinal tract. This is therefore the most common site of involvement outside the urogenital tract. A comprehensive review of the world literature on gastrointestinal malakoplakia has been made and the characteristic features of the condition have been delineated. There was a bimodal age incidence with a small cluster of cases occurring in childhood and associated with significant additional systemic disease. In the adult cases the average age was 57 years with a slight excess of males. The most commonly involved part of the gastrointestinal tract was the colon and colonic carcinoma was the most common associated disease.

Introduction
Malakoplakia is characterized microscopically by the accumulation of tissue macrophages containing unique intracytoplasmic calcified inclusion bodies. These are called Michaelis-Gutmann (MG) bodies after the authors who originally described the condition (Michaelis and Gutmann, 1902). The Michaelis Gutmann body is a rounded structure and often exhibits a concentric-ringed or targetoid reaction with a basic dye such as haematoxylin.

Malakoplakia most commonly affects the mucosa of the urinary bladder (Voight, 1958) but involvement of structures outside the urogenital tract is being reported with increasing frequency. Such sites include colon (Terner and Lattes, 1965), skin (Arul and Emmerson, 1977), breast (DiLeo and Anastasi, 1969), lungs and skeleton (Gupta, Schuster and Christian, 1972) and brain (Mirra, 1971).

The finding of malakoplakia in association with 3 cases of colonic carcinoma prompted a description of these cases and a review of the available world literature on malakoplakic disease of the gastrointestinal tract.

Case reports and pathological findings
Case 1. This was a 79-year-old man who initially sought medical aid for frequent loose bowel actions. There were no other symptoms and no significant past medical history. Sigmoidoscopy revealed an ulcerated tumour 70 mm above the anus. A biopsy confirmed the presence of an adenocarcinoma of colonic origin. Subsequently an abdomino-perineal excision of the rectum was performed and the patient is alive and well 2 years after this operation.

The resected specimen was a segment of rectum and anus 320 mm in length. There was a fungating tumour 60 mm in diameter and 30 mm in height and situated 100 mm from the distal margin. The tumour extended into the bowel wall and there were numerous soft yellow abscess-like areas in the adjacent fat and also in a separately submitted portion of presacral tissue.

Histologically, these latter areas were composed of large numbers of macrophages containing round laminated basophilic inclusions (Michaelis-Gutmann bodies). Lymphocytes, plasma cells and occasional polymorphonuclear granulocytes were also present. The tumour was an adenocarcinoma of moderate differentiation, primary to the site and had deeply invaded the muscle coats. The tumour was surrounded by a heavy acute on chronic inflammatory infiltrate with background fibrosis and large areas composed of macrophages containing typical MG bodies (Fig. 1).

Tumour permeation of lymphatic channels was not noted and the drainage lymph nodes showed a sinus histiocytosis. Some of the nodal macrophages contained MG bodies (Fig. 2).

The yellow nodules present in fat adjacent to the colon and in the presacral tissue were composed of aggregates of malakoplakic cells.

Case 2
The second case was that of a 73-year-old man who presented with a history of rectal bleeding accompanied by some loss of appetite and a little weight loss over a 3-month period. There was nothing of relevance in the past medical history. Rectal examination revealed a tumour on the left side and therefore an anterior resection with defunctioning...
colostomy was performed. The postoperative course was complicated by pulmonary embolism. The patient survived this but died after one year as a consequence of disseminated malignancy and an Escherichia coli bacillaemia (proved by blood culture).

The resected specimen was a portion of rectum and sigmoid colon 360 mm in length. Arising 30 mm from the distal limit was a 40 mm in diameter ulcerating tumour and 90 mm proximal to this there was another polyloid tumour also 40 mm in diameter. Microscopically both lesions were moderately differentiated adenocarcinomas of bowel origin. Both tumours had invaded deeply into the bowel wall reaching the serosal surface. There was a marked stromal inflammatory reaction to each tumour with infiltrations of polymorphs, lymphocytes, plasma cells and striking numbers of macrophages many of which contained typical MG bodies. The drainage lymph nodes in this case also showed a sinus histiocytosis but the nodal macrophages did not contain MG bodies.

Case 3

The third case was that of a 59-year-old woman who died 3 months after her initial admission to hospital. At that time she gave a history of right upper abdominal quadrant pain of 2 weeks' duration. Additionally there was a 10- to 12-month history of vague malaise, anorexia and moderate weight loss. In the course of extensive investigation, a liver scan revealed multiple areas of reduced isotope uptake and a follow-up liver needle biopsy showed the presence of a moderately differentiated mucin-secreting adenocarcinoma. A suggestion was made that, inter alia, a likely primary site was the gastrointestinal tract. Investigation of this failed to reveal a primary tumour.

Post-mortem examination revealed a small polypoid tumour of the rectum not associated with stenosis. There were massive secondary deposits in the liver and smaller metastases in the right lung. There was also a small adenomatous polyp of the sigmoid colon. Microscopically the rectal tumour was a moderately well differentiated mucin-secreting adenocarcinoma. It has penetrated the full thickness of the bowel wall to reach the serosal surface. In the stroma of the tumour, there was an exuberant inflammatory infiltration (Fig. 3) by polymorphs, lymphocytes, plasma cells and numerous macrophages again containing MG bodies.

In the 3 cases, the MG bodies were uniformly positive in reaction to the von Kossa (Fig. 4) and alizarin red S technique. Many, but not all, gave

Fig. 1. Malakoplakic macrophages and acute inflammatory cells in proximity to infiltrating adenocarcinoma (top right) (HE, ×100).
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Fig. 2. Michaelis-Gutmann (MG) body (arrowed) within a macrophage in a lymph node (HE, × 400).

Fig. 3. Malakoplakic macrophages admixed with acute inflammatory cells against a background of vascular granulation tissue (HE, × 200).
a positive reaction to Perls' Prussian blue stain. The MG bodies were uniformly positive with the PAS (with and without diastase) stain and this staining also revealed numerous smaller granules in the cytoplasm of macrophages. In addition to being smaller, these granules did not have the typical targetoid appearance of MG bodies. The application of both the Gram and Ziehl-Neelsen stains failed to reveal the presence of bacteria in any of the cases. EM studies were performed on material from the first case. These confirmed the presence of MG bodies but failed to reveal the presence of either intact or degenerating bacteria. Microbial cultures were not performed in any of the cases.

In the third case, the MG bodies were less numerous than in the first 2. In addition, focal irregular areas of calcification were present in the lumina of tumour glandular structures of the third case and these deposits were in association with mucin elaborated by the tumour cells.

**Review of the literature and discussion**

In addition to the 3 cases of colonic malakoplakia described herein, there are 31 recorded cases of disease involving the gastrointestinal tract (Terner and Lattes, 1965; Quijano et al., 1965; Yunis et al., 1967; Finlay-Jones, Blackwell and Papadimitriou, 1968; Kuzma, 1967; Rwylin, Ravel and Hurwitz, 1969; Blackshear, 1970; DiSilvio and Bartlett, 1971; Dockerty, 1972; Filotico and Renda, 1971; Birkenstock and Louw, 1972; Ranchod and Kahn, 1972; Wilkey and Rubel, 1972; De La Garza et al., 1973; Galian et al., 1973; Lou and Teplitz, 1973; Lewin et al., 1974; Robert, Lagace and Delage, 1974; Sanusi and Tio, 1974; Clarke, Korbel and Maher, 1975; Scheiner et al., 1975; Sinclair-Smith, Kahn and Cywes, 1975; Taghinia and Amiri, 1976; Joyeuse et al., 1977; Boixeda, Hernandez Ranz and Moreira, 1978; MacKay, 1978; Nakabayashi et al., 1978; Chaudhry et al., 1979). The presented data on each case are of variable completeness. In 33 cases (including the 3 documented herein), both age and sex are stated. A bimodal age incidence is noted comprising a group of children (below the age of 13 years) and a group of middle-aged adults. Taking both groups together, there are 19 males and 14 females and the average age is 47·54 years with a range from 6 weeks to 88 years. In the childhood group, there are 4 males and 2 females and the average age is 5·63 years (range 6 weeks to 12 years). In the adult group, there are 27 cases (no age/sex data are given for one) and the group is composed.
of 15 males and 12 females. The average age is 57 years with a range from 18 to 88 years. The racial background is 26 Caucasian and 6 non-Caucasian. Thirteen cases have emanated from the U.S.A., 6 from Australia, 4 from France, 2 from Mexico, 2 from South Africa and one each from Canada, Iran, Italy, Japan, Papua/New Guinea, Spain and the United Kingdom.

In the 34 documented cases, there was a total of 86 sites involved by malakoplakia. This figure included 63 involved sites in the gastrointestinal tract per se, 12 sites in adjacent structures (mesentery, drainage lymph nodes and retroperitoneum) and 11 sites of involvement in unrelated organs and tissues. The most commonly involved site was the colon and the least common, the anal canal (Table 1). Of the 4

<table>
<thead>
<tr>
<th>Site of involvement</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>18</td>
<td>28-57</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>12</td>
<td>19-04</td>
</tr>
<tr>
<td>Caecum</td>
<td>6</td>
<td>9-52</td>
</tr>
<tr>
<td>Descending colon</td>
<td>6</td>
<td>9-52</td>
</tr>
<tr>
<td>Ileum</td>
<td>5</td>
<td>7-94</td>
</tr>
<tr>
<td>Stomach</td>
<td>4</td>
<td>6-35</td>
</tr>
<tr>
<td>Appendix</td>
<td>4</td>
<td>5-35</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>3</td>
<td>4-76</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>2</td>
<td>3-17</td>
</tr>
<tr>
<td>Entire colon</td>
<td>2</td>
<td>3-17</td>
</tr>
<tr>
<td>Anal canal and perianal region</td>
<td>1</td>
<td>1-59</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Drainage lymph nodes</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Mesentery</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Psoas muscle</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
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<tr>
<td>Adrenal</td>
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<td>Kidney</td>
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<tr>
<td>Prostate</td>
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<tr>
<td>Anterior abdominal wall and inguinal</td>
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<td></td>
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<tr>
<td>region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

In 8 cases, there was extension of the malakoplakia process outside the immediate confines of the gastrointestinal tract with involvement of the retroperitoneum in 6 (Terner and Lattes, 1965; Birkenstock and Louw, 1972; Ranchod and Kahn, 1972; Clarke et al., 1975; Sinclair-Smith et al., 1975), the drainage lymph nodes in 4 (Quijano et al., 1965; Wilkey and Rubel, 1972; MacKay, 1978), and the mesentery in one case (Wilkey and Rubel, 1972). Involvement of somewhat more distant organs and tissues was noted in 11 cases. The urinary bladder was involved in 4 (Lou and Teplitz, 1973; Clarke et al., 1975; Joyeuse et al., 1977; Boixeda et al., 1978). The pancreas was involved in one case (Sinclair-Smith et al., 1975) and this is the only recorded case of malakoplakia of the pancreas. The adrenal was also involved in this case. Malakoplakia of the left kidney and psoas muscle was seen in continuity with disease of the descending colon in the case reported by Clarke et al. (1975). Involvement of the psoas muscle was also described by Chaudhry et al. (1979). There was prostatic involvement in the case of Boixeda et al. (1978) and disease of the anterior abdominal wall and both inguinal regions was present in the case reported by Lewin et al. (1974).

In 29 cases, other diseases were reported in association with the malakoplakia. These diseases are listed in Table 2. The most common associated disease was carcinoma of the colon (19-35%) with carcinoma of the rectum second (16-13%). Taking into account other forms of neoplasia, there was associated malignant disease in 48-4% of cases.

In the childhood cases, there was a combined immunodeficiency state characterized by diminished serum IgG, a vestigial thymus and hypoplasia of lymph nodes due to absence of germinal centres in one case (Lou and Teplitz, 1973). In another case, there was a poorly differentiated myeloid leukaemia with a probable multisystem storage disease (Sanusi and Tio, 1974). In a third case, there was pulmonary tuberculosis with systemic miliary spread (Sinclair-Smith et al., 1975). In one other case (Taghinia and Amiri, 1976) of childhood disease, there was a suspected lymphoma of the stomach and small intestine (although the only suggested evidence for this was a gastric mucosal hyperplasia seen at X-ray!) and in another case, a lymphoid hyperplasia of the colon was stated to be present, although this was not satisfactorily specified or illustrated (Kuzma, 1967). It is, therefore, evident that colonic malakoplakia is often associated with significant other disease and this is a particular feature of the childhood cases.

The duration of symptoms in adults was markedly variable ranging from 3 weeks to 2 years. Diarrhoea was recorded in 12 cases, abdominal pain in 11,
rectal bleeding in 9, signs of intestinal obstruction in 3, vomiting and malaise in 2, and fever, cough, constipation and malaise in one case each. In children, diarrhoea and rectal bleeding were recorded in 4 cases. There was fever in 3 cases, abdominal pain in 2 and failure to thrive in one.

The clinical manifestations of the adult group included a rectal tumour in 6 cases, an abdominal mass in 5, abdominal tenderness in 5, signs of weight loss in 3, and abdominal distension in one. The clinical manifestations in the childhood group were somewhat more dramatic. There was rectal bleeding, abdominal pain, fever and facial oedema in one case (Quijano et al., 1965); failure to thrive, chronic illness, fever and diarrhoea in the second (Kuzma, 1967), and chronic illness and wasting in the third (Lewin et al., 1974). A fourth case exhibited acute renal failure, rectal bleeding, haemorrhoids, fever, diarrhoea, frontal bossing, a skin rash and hepatosplenomegaly (Sanusi and Tio, 1974). In the fifth case, there was bronchitis, bloody diarrhoea, a mass in the left loin and moniliasis of mucous membranes (Sinclair-Smith et al., 1975). The final case was least dramatic with some left-sided abdominal tenderness and a vague impression of a mass at that site (Taghinia and Amiri, 1976).

In adults, carcinoma of the colon was diagnosed clinically in 9 cases and a colonic polyp in 2. Ulcerative colitis was diagnosed in 2 cases (Birkenstock and Louw, 1972; Boixeda et al., 1978) and this diagnosis was accurate in one of these (MacKay, 1978). Intestinal obstruction of uncertain cause was considered in 2 cases (De La Garza et al., 1973; Lou and Teplitz, 1973) and Crohn's disease was diagnosed in one (Birkenstock and Louw, 1972). A renal neoplasm was diagnosed in one case (Clarke et al., 1975) and leiomyosarcoma was suspected in another (Birkenstock and Louw, 1972). 'Reticulum cell sarcoma' (Gallian et al., 1973) and diffuse lymphocytic lymphoma (Lewin et al., 1974) were each known to be present in one case and the clinical impression was that of involvement of the gastrointestinal tract by these diseases. Alcoholic cirrhosis with bleeding oesophageal varices were suspected in one case (Chaudhry et al., 1979), In only one instance was malakoplaia diagnosed by biopsy before major therapeutic intervention.

In the childhood cases, there was a diagnosis of carcinoma in one case (Ranchod and Kahn, 1972) and colonic polyposis in another (Kuzma, 1967), while an immunodeficiency state (? chronic granulomatous disease of childhood) was suspected in a third (Lou and Teplitz, 1973). The fourth case was diagnosed as renal failure due to a storage disease (Sanusi and Tio, 1974), while the fifth was considered to have a neuroblastoma, peri-adrenal haemorrhage and Wolman's disease (Sinclair-Smith et al., 1975).

In 12 of the adult cases, there was a surgical excision of the diseased portion of the gastrointestinal tract before diagnosis was established. In 7 cases, there was a history of pre-operative systemic treatment with corticosteroids, 2 cases of treatment with antibiotics and one of treatment by radiotherapy.

Macroscopically the lesions, other than obvious malignant tumours, were most commonly described as being yellow in colour and in 13 cases there was more than one macroscopic lesion. In 9 cases, colonic nodules of varying size were described. Polyps were described in 6 cases, and in one, the malakoplakia process involved the stroma of a villous adenoma. Gastric mucosal nodules (Yunis et al., 1967; Scheiner et al., 1975) were present in 2 cases. Irregular colonic zones, a soft appendicular serosal plaque, a rounded colonic serosal mass, a tumour mass, induration of the bowel wall, fistulae, mucosal plaques, stenotic colonic lesions, thickened gastric mucosa and chronic ulcerative colitis with pseudopolyposis were each described in one case.
Microscopically Michaelis-Gutmann bodies were described in all cases, but in 3 (Scheiner et al., 1975), no histochemical details were given. The von Kossa reaction was positive in 25 cases and negative in one (Blackshear, 1970). The PAS stain (variably with or without prior diastase digestion) was positive in 26 cases and the Perls' Prussian blue reaction for iron was positive in 20. Only in a small number of cases was a more extensive histochemical study performed. Oil red O staining was performed and positive in 3 cases. Ziehl-Neelsen staining was negative in 5 cases. The Gram stain was applied in 8 cases with the finding of Gram-negative bacilli in 3 of these. Luxol fast blue and Sudan stains were positive in the 2 cases tested. The alizarin red S technique was positive in 4 cases. Giemsa, acid phosphatase and Alcian blue stains were each positive in the one case tested. In these instances, the MG bodies gave the positive reactions. Immunoperoxidase techniques showed the presence of human IgA, IgM and muramidase in the malakoplakic macrophages of one case (MacKay, 1978).

Micro-organisms were sought in 16 cases. In 3, culture of diseased tissue was performed. *E. coli* and *Aerobacter aerogenes* were recovered in one case (Terner and Lattes, 1965). *E. coli* (0:25 : 1315) in another (Arul and Emmerson, 1977) and *E. coli* and *Klebsiella pneumoniae* in a third (Sinclair-Smith et al., 1975). In 8 cases, Gram staining of histological sections was done. In one case, occasional Gram-negative rods were not associated with MG bodies by electron microscopy (Finlay-Jones et al., 1968). In 2 cases, macrophages contained Gram-negative bacilli and in one of these, EM showed intracellular bacteria (Yunis et al., 1967; Lou and Teplitz, 1973). In 5 cases, Gram stains were negative and in one of these, Giemsa staining showed no organisms and in 4 cases, Ziehl-Neelsen staining was negative. In one of the former cases, bacilli similar to *E. coli* were alleged to be present on the basis of electron microscopical findings (MacKay, 1978). Of the remaining cases, there was thought to be rod-shaped bacilli in malakoplakic cells by HE staining in one case, but this was not substantiated by Gram staining (Yunis et al., 1967). In another case, *E. coli*, *Pseudomonas aeruginosa*, *K. pneumoniae* and *A. aerogenes* were isolated from the faeces (De La Garza et al., 1973). Finally, in 2 cases partly digested intracellular bacteria were seen on electron microscopy (Nakabayashi et al., 1978; Chaudhry et al., 1979).

Considering the past or more recent medical history of patients with malakoplakia of the gastrointestinal tract there are interesting backgrounds in 9 of the adult cases and 3 of the childhood cases. In one adult case, there were numerous previous non-specific illnesses, an excision of a thymoma, asthma and a peptic ulcer (Terner and Lattes, 1965). Another patient had a systemic disorder? rheumatoid arthritis, ? systemic lupus erythematosus and proved pulmonary nocardiosis (Blackshear, 1970). A third case had prostatic carcinoma, atrial fibrillation and severe generalized atherosclerosis (Dockerty, 1972). One patient had a diffuse poorly differentiated lymphocytic lymphoma and there was also a proved urinary tract infection with *E. coli* (Lewin et al., 1974). One other case had an *E. coli* urinary infection and there was also an old pulmonary tuberculosis in this case (Clarke et al., 1975). A small group of cases had long-standing diseases of the gastrointestinal tract. Thus there was a case of recurrent villous adenomata (Robert et al., 1974), a case of episodic intestinal obstruction, peritonitis, urinary fistulae and abscess formation (Joyeuse et al., 1977) and a case of chronic ulcerative colitis with a history of cervical lymph node tuberculosis many years previously and currently exhibiting a high antibody titre to *E. coli* and with reduced T-lymphocytes (MacKay, 1978). In the case reported by Chaudhry et al. (1979), there was alcoholic cirrhosis complicated by portal hypertension and oesophageal varices. In the childhood group of cases, one had a year-long history of diarrhoea, another exhibited para-cortical lymphoid depletion in the peri-adenal lymph nodes and in the third, there was a family history suggestive of immune deficiency.

Therefore a consideration of malakoplakia as it affects the gastrointestinal tract indicates 2 essential groups of cases. One group has malignant colonic or rectal tumours in which the malakoplakic process is a local stromal phenomenon. The 3 cases reported herein belong to this group. In the second group, the malakoplakia is often more extensive and there is usually a systemic disease perhaps implying a more generalized disorder of macrophage and/or immune function.

There would appear to be a substantial association between *E. coli* infection and gastrointestinal malakoplakia but the association is by no means an absolute one. In only one instance (Terner and Lattes, 1965) has histochemical evidence been adduced to support the hypothesis that the matrix of the MG body contains non-mammalian (presumably bacterial) glycolipid. Kerr et al. (1972) in a chemical analysis of prostatic tissue from a case of prostatic malakoplakia were unable to demonstrate non-mammalian components in their analysis. Against this, renal malakoplakia may apparently be induced in the experimental animal by the injection of crude lipopolysaccharide extract (Boivin antigen) of *E. coli* (Csapo et al., 1975). The presence of either intact or disintegrating bacilli in phagosomes within macrophages is not conclusive evidence of a causal role of *E. coli* derivatives in the genesis of malako-
plakia since whatever the fundamental lesion of the macrophage in malakoplakia, phagocytic activity may be normal and the presence of bacilli thereby coincidental.

It has been suggested (Editorial, 1978) that malakoplakia may be an expression of microtubular/microfilamental dysfunction. The intracellular system of microtubules and microfilaments is thought to be concerned with several cellular functions, including active movement. In the cases reported herein, malakoplakic cells were noted in drainage lymphs and there had also been extension into the retroperitoneum. One wonders if active movement is a component of this extension of the malakoplakic process, and, if it is, then that aspect of microtubule/microfilament function would not be disordered.

From the viewpoint of accurate histodiagnosis then obviously conspicuous aggregations of macrophages require close inspection and, if necessary, special stains to demonstrate the characteristic MG bodies. However, it is worth emphasizing that in the 3 current cases, the inflammatory infiltration was mixed containing appreciable quantities of inflammatory-type cells other than macrophages. Perhaps local stromal malakoplakia in association with gastrointestinal neoplasia has been underdiagnosed because of lack of appreciation of the fact that malakoplakic macrophages may be part of a mixed acute and chronic inflammatory cell infiltration.

References


Mackay, E.H. (1978) Malakoplakia in ulcerative colitis. Archives of Pathology and Laboratory Medicine, 102, 140.


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