

*CASE REPORT*

**Intra-abdominal, crystal-storing histiocytosis due to clofazimine in a patient with lepromatous leprosy and concurrent carcinoma of the colon**

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*Summary* We report a case with abdominal complications of clofazimine treatment which included blackish discolouration of the lymph nodes, omentum and peritoneum. A 44-year-old female with lepromatous leprosy and a history of adverse reaction to clofazimine 2 years previously, presented with rectosigmoid junction adenocarcinoma. Laparotomy revealed an inoperable tumour with pigmentation of the bowel, serosa and peritoneum. A second operation had to be performed for transverse loop colostomy and a mesenteric lymph node biopsy sent for frozen section showed typical clofazimine crystals. Despite widespread use for many years in the treatment of leprosy, this drug is not known to be carcinogenic and this case provides no evidence for an association or link between its use and the patient's cancer. Apart from its use in leprosy, clofazimine may be used in the treatment of disseminated *Mycobacterium avium-intracellulare* infection, Buruli ulcer due to *M. ulcerans* and occasionally in other mycobacterial infections. An awareness of the rare side-effect described above may help in the clinical assessment and management of such cases, including the avoidance of unnecessary laparotomy.

**Case report**

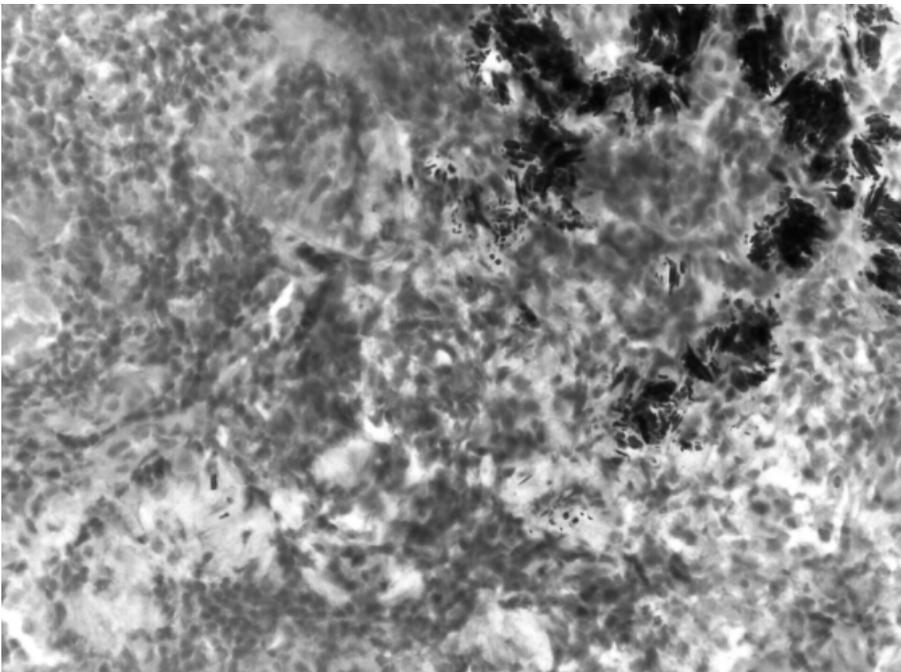
A 44-year-old Indian female patient presented at St John's Medical College Hospital, Bangalore, India in September 2002 with acute pain in the lower abdomen for 15 days and bleeding per rectum for 4 days. Sigmoidoscopy showed a fungating ulcerated mass suggestive of malignancy but not conclusive on biopsy (because of superficial necrosis). The patient was not in obstruction and could pass normal stools, but had lost about 6 kg in the last 2 months. She had been treated with multidrug therapy for multibacillary lepromatous leprosy from September 1998. Treatment was stopped in March 2000, but restarted in April 2001. She had symptoms of mild pain in the abdomen and dark discolouration of the skin

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from June 2000 onwards, i.e. 3 months after stopping first treatment. The second period of treatment was stopped in May 2002.

An exploratory laparotomy for the cancer was performed and it was found to be unresectable. Intraoperative biopsy was taken from a metastasis to the liver, along with blackish discoloured tissue from the omentum and from the blackish discoloured mesenteric lymph nodes. The biopsy from the liver showed adenocarcinoma and the mesenteric lymph node showed evidence of lipofuscin-like pigment on routine paraffin section histopathology. After fixing in 10% formalin, the lymph node appeared pale brown and the omentum did not show any blackish areas. Sections from the lymph node showed reactive hyperplasia with sinus histiocytosis with a brown pigment that gave staining reactions of lipofuscin, i.e. it was strongly PAS positive, weakly acid-fast with the Ziehl–Neelsen technique. Histological examination of the omentum showed no pigment. It was concluded that the pathological findings in the abdomen were due to the deposition of clofazimine crystals.

At a later date, the patient had intestinal obstruction and a transverse loop colostomy was performed with excision of a mesenteric lymph node for frozen section. Clinically, the colour of the mesenteric lymph nodes and the omental staining suggested clofazimine as the cause, but might have been interpreted as transit lesions from an anorectal melanoma. The second mesenteric lymph node biopsy was sent without a fixative for frozen section and haematoxylin & eosin (H&E) stained sections showed sinus histiocytosis with dark brown pigment in the histiocytes. This pigment showed bright-red birefringence with polarized light. Unstained frozen sections were also viewed with polarized light and showed much larger amounts of the bright red birefringent crystals (Figure 1). Parts of the lymph node were also processed by



**Figure 1.** Mesenteric lymph node removed at laparotomy showing sinus histiocytosis with accumulations of dark brown pigment and bright red, birefringent crystals with polarized light. Original magnification  $\times 400$ .

paraffin sections. H&E stained sections showed sinus histiocytosis with minimal brown pigment within them and the same staining reactions as in the previous biopsy.

The patient recovered well after the colostomy. At the time of writing (early 2003), the colostomy is functioning well and the patient is symptomatically better.

## Discussion

Fourteen other cases of clofazimine enteropathy have been reported in world literature (English),<sup>1-14</sup> as summarized in Table 1. Over 70% of patients underwent exploratory laparotomy, the indications for which included acute abdomen, subacute intestinal obstruction, acute mesenteric ischaemia and perforated duodenal ulcer. The indication in our case was for unrelated, but associated rectosigmoid cancer.

The total amount of clofazimine received at the onset of abdominal pain varies from 9 g to 657 g, and the highest dosage ranges from 600 mg per week to 600 mg per day. The onset of abdominal pain ranges from 82 days to 8 years after treatment.

The granular amorphous material in histiocytes described by Jagadesan *et al.*<sup>2</sup> concurs with the characteristic sequence of clofazimine following oral administration described by Conalty *et al.*<sup>15</sup> The lipophilic riminophenazine compound appears initially in the cytoplasm of histiocytes as orange-red bodies (drug-containing phagosomes), 0.5–2 µm in diameter. Later, gradual replacement of drug inclusions by clofazimine crystals is evident. The actual time interval at which these inclusions are seen varies according to the organ and depending upon the drug concentration in the tissue. The clofazimine crystals in histiocytes are identical to those in the drug, confirmed by spectrophotometry in humans.<sup>16</sup>

The histological findings of crystal-storing histiocytosis associated with marked interfollicular plasmacytosis are associated with B-cell neoplasms such as multiple myeloma and lymphoplasmacytic lymphoma.<sup>17</sup> Some of the earlier publications on the use of clofazimine expressed concern that the striking intracytoplasmic accumulation of crystals in human tissues over a long period of time might be carcinogenic, but a review of the literature gives no support for this, despite the widespread use of this drug for leprosy over several decades. The findings in the case described above give no basis for a link or association between the use of clofazimine for the patient's leprosy and the development of bowel cancer.

From a surgical point of view, the intra-abdominal manifestations should not be mistaken for melanoma of the anorectum with spread to omentum and mesenteric lymph nodes. Furthermore, since clofazimine may be used for the treatment of disseminated *Mycobacterium avium-intracellulare* infection, Buruli ulcer due to *M. ulcerans* and occasionally for the treatment of other mycobacterial infections, surgeons should be aware of the rare side-effects described above in the clinical assessment and management of such cases, including the avoidance of unnecessary laparotomy.

## References

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**Table 1.** Fourteen cases of clofazimine enteropathy previously reported in the world literature

References (type of report)	Age/sex (race)	Underlying disease	Highest dosage of clofazimine	Total amount taken at the onset	Onset/duration of symptoms	Abnormal X-ray	Confirmation of crystals	Exploratory laparotomy	Results
Atkinson <i>et al.</i> (1967) <sup>1</sup> (full paper)	19/M (Mexican)	Lepromatous leprosy	600 mg/day	~108 g	6 months after treatment/8 months	Yes	Yes	No	Mild abdominal symptoms; still on 300 mg/day
Jagadeesan <i>et al.</i> (1975) <sup>2</sup> (full paper)	32/M (Indian)	Tuberculoid Leprosy	100 mg/day	9 g	3 months after treatment/5 days	No	No	Yes	Relieved within 2 weeks after stopping the drug
Desikan <i>et al.</i> (1975) <sup>3</sup> (full paper)	22/F (Indian)	Lepromatous leprosy	300 mg/day	36 g	NA/4 months	NA	Yes (autopsy)	No	Died 1 month later after stopping the drug; systemic amyloidosis found at autopsy
Karat (1975) <sup>4</sup> (full paper)	NA (2 cases)	Leprosy	300 mg/day	NA	6 months & 18 months after treatment/NA	Yes	Yes	Yes	Relieved within 8–10 weeks after stopping the drug
Joplin (1976) <sup>5</sup> (editorial)	Adult/M (NA)	Lepromatous leprosy	200 mg/day (57 months)	~199 g	34 months after stopping the drug/12 months	No	Yes	Yes	NA
Harvey <i>et al.</i> (1977) <sup>6</sup> (abstract)	Adult/F (Burmese)	Lepromatous leprosy	600 mg/day (6 years)	~657 g	3 years after treatment/7 years	NA	Yes (autopsy)	No	Died of acute electrolyte imbalance following acute abdomen 4 years after stopping the drug
Mason <i>et al.</i> (1972) <sup>7</sup> (full +paper)	29/F (Samoan)	Lepromatous leprosy	600 mg/day	657 g	3 years after treatment/6 months	Yes	Yes	Yes	Severe abdominal pain after stopping the drug and 6 months later; periodic pain controlled by simple analgesics
Bryceson (1979) <sup>8</sup> (Letter to the editor)	24/M (Indian)	Lepromatous leprosy	500 mg/day	~34 g	82 days after treatment/1 month	NA	Yes	Yes	Relieved after stopping the drug

McDougall <i>et al.</i> (1980) <sup>9</sup> (full paper)	68/M (NA)	Pyoderma gangrenosum	400 mg/day	~14 g	11 months after treatment/7 months	NA	Yes	Yes	Well after operation; died of cardiac arrest 6 weeks later; no autopsy
De Bergeyck <i>et al.</i> (1980) <sup>10</sup> (full paper)	38/F (Italian)	Chronic ulcer ( <i>Mycobacterium ulcerans</i> )	300 mg/day	9 g	3 months after treatment/7 months	Yes	No	No	Well after operation; normal X-ray 14 months later
Belaube <i>et al.</i> (1980) <sup>11</sup> (full paper)	46/F (NA)	Prurigo nodularis	300 mg/day (6 months)	54 g	10 months after stopping the drug/22 months	NA	Yes	Yes	Relieved after on a gluten-free diet and stopping the drug
Venencie <i>et al.</i> (1986) <sup>12</sup> (Letter to the editor)	47/F (NA)	Lepromatous leprosy	200 mg/day	342 g	54 months after treatment/3 months	Yes	Yes	Yes	Relieved after on a gluten-free diet and stopping the drug
Chong and Ti (1993) <sup>13</sup> (full paper)	41/M (Chinese)	Leprosy	600 mg/week	249.6 g	8 years after treatment/2 years	Yes	Yes	Yes	Well after operation
Sukpanichant <i>et al.</i> (1998) <sup>14</sup>	32/M (Thai)	Leprosy	300 mg/day (15 months)	113.6 g 600 mg/day	3 months after stopping the drug/2 years	Yes	Yes	Yes	Died 2 months after laparotomy; had an acute onset of dyspnoea; no autopsy
Present case (2002) (full paper)	44/F (Indian)	Lepromatous leprosy, bipolar affective disorder, carcinoma rectum grade 4	300 mg/day	101.9 g	3 months after stopping first treatment/3 years	No	Yes	Yes	Patient is with transverse loop colostomy which is functioning well

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