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Pathology of intestinal tuberculosis and its distinction from Crohn’s disease

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SUMMARY Intestinal lesions of 212 cases presenting with symptoms of intestinal obstruction were studied. Of these, 159 cases were diagnosed as tuberculosis and 10 as Crohn’s disease. Forty-three cases could not be classified into any of these entities and are excluded from this account. The amount of chemotherapeutic drugs received by each patient preoperatively was recorded. Cases proved as tuberculosis at the first operation were put on antituberculosis chemotherapy. Thirteen of these cases were operated on a second time, and tissue reactions under the influence of chemotherapy were studied. Fresh diseased tissue was studied for acid-fast organisms by culture and animal inoculation.

Morphological features of the tuberculosis group are described in detail. Although the cases were broadly classified into the ulcerative and ulcerohypertrophic varieties, a distinction was not always sharp and the two types of lesions were at times found to coexist. The macroscopic features presented a very wide range, and at times distinction from Crohn’s disease, especially in the ulcerohypertrophic variety, was difficult. Microscopically, however, they could be distinguished without much difficulty. Caseation, although a characteristic feature of tuberculous granulomas may, albeit rarely, be absent. Granulomas which are characteristically confluent may be present only in the mesenteric lymph nodes. Acid-fast organisms are not grown consistently from diseased tissues; where grown, they are of human type. Reparative changes during chemotherapy are described in detail; these follow a non-specific pattern.

In the group of Crohn’s disease, transmural cracks and fissures were consistently observed in all cases. Distinguishing features between the two diseases are discussed in detail.

After the classical description by Crohn, Ginzburg, and Oppenheimer (1932) of regional enteritis the term ‘hypertrophic ileocaecal tuberculosis’ was all but discarded (Taylor, 1945; Anand, 1956; Bruce, 1959; Rhoades, Klein, and Welsh, 1960; Chandra and Basu, 1967), and its authenticity began to be doubted (Paustian and Brockus, 1959). In its over-enthusiastic acceptance, even workers in countries where tuberculosis is still prevalent claimed that cicatrizing lesions in the ileocaecal region were in fact Crohn’s disease (Mangalik and Misra, 1952; Gupta, Chatterjee, Roy, and Ghosh, 1962). Figures for the incidence of the two diseases from the same country show a wide variation (Tribedi and Gupta, 1941; Anguli and Menon, 1950; Banerjee, 1950; Mangalik and Misra, 1952; Anand, 1956). This is perhaps due to relatively inadequate studies made on small series of one to 15 cases (Ashken and Baron, 1962; Amerson and Martin, 1964; Howell and Knapton, 1964; Lee and Roy, 1964; Winter and Goldman, 1966) and difficulty in distinguishing the morphological features of tuberculosis and Crohn’s disease (Taylor, 1945; Cattell and Mosely, 1946; Warren and Sommers, 1948; Hoon, Dockerty, and Pemberton, 1950; Anand, 1956; Brenner, Annes, and Parker, 1970).

Perhaps the most detailed account of the pathology of ileocaecal tuberculosis has been given in the often quoted paper by Hoon et al (1950). Among the 58 cases studied by them, they described the entity of ‘non-caseating tuberculated enterocolitis’ which resembled tuberculosis, but neither showed caseation in the granulomas nor yielded organisms on culture.
The terminology has created considerable confusion and has not been accepted by subsequent workers. While investigating a large series of cicatizing intestinal lesions of inflammatory origin, the clinical and radiological features of which have been reported earlier (Prakash, Tandon, Nirmala, Wadhwa, Prakash, and Kapur, 1970), we have been impressed by the protein anatomical manifestations of intestinal tuberculosis. The present communication is a detailed account of our experience with these pathological features and their differentiation from Crohn's disease.

Material and Methods

Two hundred and twelve patients presenting with symptoms of chronic or subacute intestinal obstruction were studied. The amount and type of chemotherapy received by each patient was recorded. The operation consisted generally of resection of the diseased segment of the intestine with the mesenteric lymph nodes, or, where this was not possible, a biopsy of the diseased tissue. In many cases, fresh biopsy material from the diseased tissue was submitted for bacteriological examination and culture, and a tissue homogenate was used for a guinea pig inoculation test. Patients diagnosed histologically as tuberculous were put on a course of antituberculosis chemotherapy consisting usually of streptomycin 1 g and isonicotinic acid hydrazide (INH) 300 mg daily for 90 days followed by para-aminosalicylic acid (PAS) 9 g and INH 300 mg daily for four to five months.

The present paper is based on a study of 169 cases which were diagnosed as tuberculosis (159 cases) or Crohn's disease (10 cases); the remaining 43 cases could not be classified as either of these diseases and are excluded from this account. Among the 159 cases of tuberculosis, 39 had only a biopsy at the first operation. These were put on chemotherapy and 13 of them had to be operated on a second time for recrudescence of obstructive symptoms, when a segment of intestine was resected after an interval ranging from one month to three years and two months. Thus a total of 133 specimens of resected intestine were available from the group. In the group of Crohn's disease, resected intestine was available in all the 10 cases.

Macroscopic examination was conducted after 24-hour fixation of the opened intestine. Tissue blocks were taken from the entire circumferential width of the ulcerated lesions, sliced at 5 mm intervals, and the mesenteric nodes. Histological sections were stained with haematoxylin and eosin, and where necessary, for acid-fast bacilli, reticulin, and connective tissue.

Observations

The sex distribution was predominantly female in the tuberculosis group, the female : male ratio being approximately 2:1, whereas in Crohn's disease males predominated 4 : 1. The commonest age group affected in both the groups was 20-39 years (105 out of 159 cases for tuberculosis and six out of 10 cases for Crohn's disease). Four cases in the tuberculosis group belonged to the first decade.

The commonest site of the lesion in both the groups was the lower ileum and ileocaecal region (90 out of 159 cases in tuberculosis and four out of 10 cases in Crohn's disease). Colon alone was involved in five cases of tuberculosis and one case of Crohn's disease; when considered in combination with the ileocaecal region and terminal ileum, it was involved in 18 and three cases respectively of tuberculosis and Crohn's disease. Duodenum and/or jejunum was involved in two cases of tuberculosis.

Tuberculosis

MACROSCOPIC CHANGES

The active lesions can be described under the following broad categories of ulcerative and ulcerohypertrophic types.

The ulcerative type

The diseased segment is moderately indurated and is marked by a conspicuous increase in mesenteric fat and the circumference is studded with nodules of variable size. Mesenteric lymph nodes are usually enlarged. Characteristic caseation may be found only after examining numerous lymph nodes.

The ulcers may be single or multiple, in the latter case variable lengths of uninvolved mucosa being present in between (Fig. 1). Characteristically, the established lesion consists of an annular ulcer involving the entire circumference affecting a segment generally less than 3 cm in length (Fig. 1). The lumen in this region is narrowed, sometimes measuring less than 1 cm in diameter, resulting in a napkin-ring type of stricture (Fig. 1).

Ulceration is relatively superficial and does not ordinarily penetrate the muscularis propria. The ulcers present a variable appearance. The ulcer bed is covered with a necrotic slough. It may be coarsely granular, often showing small pseudopolyps, or the mucosal folds may be replaced by a mamillated surface. Sometimes, the mucosal folds are evened out and scattered with irregularly disposed mucosal erosions. Where the ulcers are well defined, the margins may be undermined or sloping, or flush with the surface. In an occasional case, the ulcer presents a stellate appearance with a deep excavation
bordered by sharply overhanging hypertrophic mucosal shelves which are intensely hyperaemic. The ulcer in such cases tends to be disposed along the longitudinal axis and the neighbouring mucosal folds tend to converge upon the ulcer. The thickness of the wall underlying the ulcer bed is variable; it may be thinned or may appear hypertrophic and scarred, streaked with yellowish areas of necrosis.

In one case the entire mucosal surface of the caecum and the adjacent ascending colon was replaced by a ragged appearance with extensive pseudopolyposis, mucosal bridging, and deep, gutter-like ulcers running along the longitudinal axis (Fig. 2).

_Ulcero-hypertrophic variety_

This variety commonly affects the ileocaecal region, the patient presenting with a large lump in the right iliac fossa. The ileocaecal region, mesenteric fat, and their constituent lymph nodes are seen to constitute a large mass with extensive adhesions. The ileocaecal angle is distorted and often obtuse. On opening, the wall is seen to be markedly thickened, occasionally in a tubular form, measuring up to 3 cm in thickness. The mucosal changes are quite variable. There may be a prominent ‘cobblestoning’ or pseudopolyposis (Fig. 3) or the mucosal folds may be flattened and the surface shows irregularly disposed furrows mostly converging upon the constriction.

It may be mentioned here that there are no sharp differences in the two varieties described above, and the two types of lesion may coexist.

Among all the cases, including both varieties, seven had perforation of the bowel and two had faecal fistulae.
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Fig. 3 Tuberculous enteritis of the ulcerohypertrophic variety showing tubular narrowing and pronounced 'cobblestoning'.

Fig. 4 Healed tuberculous enteritis. The mucosa is completely regenerated, and the area showing smoothed folds represents the site of the old lesion. The nodular projections are prominent Peyer's patches.

Healed tuberculosis
Five cases were diagnosed as healed tuberculosis on the basis of a previous history of active tuberculosis, proved at surgery, and followed by a period of antibiotic chemotherapy, resulting in a complete disappearance of specific morphological features of tuberculosis. In such cases, the mucosa was completely regenerated and smooth, and often studded with nodules 2 to 3 mm wide representing hypertrophic Peyer's patches (Fig. 4).

Microscopic changes
Microscopic features of the two varieties do not differ significantly, the mass in the hypertrophic variety being principally contributed by exuberant granulomatous tissue extending onto the serosa, and also by mesenteric fat, enlarged lymph nodes, fibrosis, and hypertrophy of the muscularis. The first appearance of the granulomas seems to take place in the mucosa or the Peyer's patches (Fig. 5). The structure of the caseating granulomas, which is considered a diagnostic finding, is well known. The peripheral part of the granuloma contains a zone of

Fig. 5 Active tuberculous enteritis showing numerous confluent, non-caseating granulomas in the mucosa. H & E × 105.
infiltration by an admixture of lymphocytes, plasma cells, and giant cells of the Langhans variety (Fig. 6a). The granulomas are often large and usually show marked variation in size. Characteristically, they tend to be confluent and the initial focus seems to enlarge by expansion of individual granulomas or by confluence of numerous satellite granulomas (Fig. 6b).

The ulcers do not usually penetrate beyond the muscularis and are mostly lined by non-specific inflammatory granulation tissue, with the infiltrate abounding in polymorphs and often extending into the submucosa as microabscesses. Granulomas are often seen in the immediate lining of the ulcer bed. There is no appreciable widening of the submucosa although a variable degree of oedema may be observed in the vicinity of the ulcer beds with dilatation of the lymphatics. The oedema is never as severe as in Crohn's disease. Transmural cracks and fissures are generally not a conspicuous feature; if at all present, they do not extend beyond the submucosa (Fig. 7A). Such fissures are often lined by characteristic granulomas. In longstanding lesions there may be a variable degree of fibrosis which extends from the submucosa into the muscularis. The transition to the grossly uninvolved areas is gradual, well formed granulomas being observed in the wall in adjacent areas.

Many established lesions show variable degrees of reparative changes, even in cases which have not received antituberculosis chemotherapy as described later. Pyloric gland metaplasia is common and extensive, and often observed in cases with active inflammation.

A point of special emphasis is that often numerous sections of the intestinal wall show an entirely non-specific picture and the granulomas may be seen only in the regional lymph nodes. This phenomenon was
Fig. 7A  Tuberculous enteritis. A fissure runs superficially through the submucosa, and is lined by characteristic granulomas. H & E × 80.

Fig. 7B  Crohn's disease. A transmural fissure is seen to extend deep into the muscularis, almost up to the serosa. H & E × 90.

Fig. 8  Healed tuberculous granuloma in the mesenteric lymph node. H & E × 200.
observed in nine cases. Five patients had received no antituberculosis chemotherapy and the remaining four had received 7-40 g of streptomycin. The reverse, i.e., the presence of granulomas in the intestine and no granulomas in the lymph nodes, has not been observed in any case. Characteristic granulomas may be seen only in a few lymph nodes, the rest showing only a non-specific reaction associated with variable amounts of para-amyloid. Healed granulomata have been observed only in the lymph nodes. The granulomas undergoing healing tend first to be circumscribed by hyalized connective tissue and later are completely replaced by it (Fig. 8).

Tissue Changes Observed in Healing

Pathological material before and after the administration of antituberculosis chemotherapy was available only from 13 patients who were operated on twice. This material is not sufficiently large for any definite conclusions regarding the length or amount of antituberculosis chemotherapy and its relationship with the degree of tissue healing. However, five patients who had active lesions at the first operation healed completely; the ulcers had re-epithelialized, and no active granulomas were recognized in the intestine or the lymph nodes. They had received antibiotic treatment consisting of 90-200 g streptomycin in addition to PAS and INH as in the regimen stated above. The rest continued to show activity of lesions in the form of active granulomas. Among them one had received 150 g and others 30-75 g of streptomycin.

The first evidence of healing is seen as mucosal regeneration which begins at the ulcer margins, first as a single layer of mucosal cells with hyperchromatic nuclei which are seen to creep along the surface from both sides bridging over a part of the entire surface. The mucosa is reconstituted by the epithelium dipping down to form tubular glands. Later, it tends to be thrown into simple folds complete with their own muscularis mucosae and the acini dispersed in irregular axes. This accounts for the cobblestoning which is not produced by submucous oedema. In the final stages the villous pattern is more or less completely re-established. It has been seen, however, that even in such instances, occasional gaps of unbridged ulcers still remain which continue to be lined by inflammatory granulation tissue. There is a variable degree of fibrosis involving the submucosa as well as the muscularis. The intensity of the inflammatory reaction steadily diminishes. However, unlike the lymph nodes, there are no rounded scars suggestive of healed individual granulomas.

In some instances, mucosal crypts were seen embedded deep in the hypertrophic scarred muscularis. These crypts of misplaced epithelium are distended with mucin or even inflammatory infiltrates, which may be seen bursting.

The healing reaction in the lymph nodes is more precise and the pattern more predictable as described earlier.

Bacteriological Studies

Organisms were grown from 15 cases, of which three had shown no positive microscopic findings characteristic of the disease either in the bowel or the regional lymph nodes on initial examination. A subsequent examination of further tissue blocks revealed characteristic granulomas in one case. In three other cases no caseation was observed in the granulomas. One patient had received 150 g of streptomycin before the resection of the specimen which yielded a positive culture. A guinea-pig inoculation test was also positive in one of these latter three patients. All organisms were of the human type.

Crohn's Disease

The morphological features of this disease are well known and have been exhaustively described (Lockhart-Mummery and Morson, 1960, 1964; Cornes and Stecher, 1961; Williams, 1964; Hawk, Turnbull, and Farmer, 1967; McGovern and Goulston, 1968; Lennard-Jones, Lockhart-Mummery, and Morson, 1968; Morson, 1968). The lesions were all chronic, and the inflammatory reaction was characteristically transmural. Irregularly disposed cracks and fissures penetrating the wall, many times through the muscularis propria, emphasized by Morson (1968) as a characteristic feature, were present in all cases (Fig. 7B). Sarcoid granulomas were observed in two cases. Figures 6 and 7 illustrate the morphological differences between the granulomas and the cracks and fissures respectively between tuberculosis and Crohn's disease.

Discussion

From the above account it is evident that tuberculosis still constitutes the most important single aetiological factor in ulcerocnstrictive lesions of the intestine in India, as also indicated in earlier reports from this country (Anguli and Menon, 1950; Banerjee, 1950; Anand, 1956; Chandra and Basu, 1967; Hancock, 1968).

Many workers (Paustian and Bockus, 1959; Hamandi and Thamer, 1965; Anscombe, Keddie, and Schofield, 1967; Bentley and Webster, 1967) have attempted to classify the lesions into ulcerative,
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ulcerohyperplastic, and hyperplastic varieties, following the classification of Hoon et al (1950). Such a strict classification is not always possible although admittedly the lesions in the ileocelecal region are often of the ulcerohyperplastic variety (Howell and Knapton, 1964).

By far the commonest site of involvement in the bowel is the terminal ileum and the ileocelecal region, as shown by the high incidence of involvement of these regions in the series (Hancock, 1958; Abrams and Holden, 1964; Bentley and Webster, 1967; Bockus, 1964). This study also confirms the belief that tuberculous colitis is by itself an uncommon disease entity, and that in the colon the most frequently observed site is the caecum, followed by the ascending and descending colon (Abrams and Holden, 1964).

Our experience with tuberculosis indicates that the clinical and gross morphological manifestations of this disease are protean, and can mimic a number of diseases. This point is emphasized with regard to the macroscopic appearance of tuberculosis, particularly affecting the ileocecal region where it may produce a tubular narrowing, longitudinal furrowing, and occasional 'cobblestoning' of the mucosa and it may be difficult to distinguish it from Crohn's disease (Fig. 3).

Hoon et al (1950) emphasize two criteria for diagnosing tuberculosis: the presence of caseating granulomas in the bowel of lymph nodes, and a positive demonstration of acid-fast organisms in tissues or in culture or a positive animal inoculation test. Undoubtedly, these criteria should be fulfilled before a lesion can be objectively accepted as tuberculosis. In the experience of the authors, all the above criteria are rarely ever satisfied in all cases. Caseation appears to bear no relationship to positive cultures (Taylor, 1945; Rappaport, Burgoyne, and Smetana, 1951; Anand, 1956; Hancock, 1958; Abrams and Holden, 1964; Howell and Knapton, 1964; Lee and Roy, 1964). It may not always be present and often one has to study a large number of sections or numerous deep cuts in the tissue block before it is seen. In three cases no evidence of caseation was found in the multiple sections examined, and in another three initial microscopic examination of the lesion was not diagnostic of the disease, yet bacterial cultures were positive in all cases. The experience of Sweany (1947), Hoon et al (1950), Ashken and Baron (1962), Howell and Knapton (1964), Chandra and Basu (1967), and Hawley, Wolfe, and Fullerton (1968) has been similar. Organisms grown were all of the human type as in the previous studies, with the exception of that of Hamandi and Thamer (1965) from Iraq.

A tubercular granuloma, the hallmark of diagnosis of tuberculosis, may at times not be evident at the initial examination, especially in the sections from the intestine, and an examination of mesenteric lymph nodes is often more rewarding. In nine cases a diagnosis of tuberculosis was made only by the presence of characteristic granulomata in the lymph nodes, none of the several sections, including deep cuts into the tissue blocks of the intestinal lesions, having shown any. Such was also the experience of Bockus, Tumen, and Kornbloom (1940), Hoon et al (1950), Hancock (1958), and Chandra and Basu (1967). In cases undergoing chemotherapy, the characteristic granulomata had often disappeared in the intestine but were present in active or healed forms only in the mesenteric lymph nodes.

MORPHOLOGICAL DISTINCTION FROM CROHN'S DISEASE

The difficulties of distinguishing Crohn's disease from tuberculous enteritis have been repeatedly emphasized (Taylor, 1945; Cattell and Mosely, 1946; Hoon et al, 1950; Anand, 1956; Brenner et al, 1970). As described and illustrated above, in tuberculosis the luminal narrowing may be tubular, as also was observed by Howell and Knapton (1964). The mucosal changes may also show a striking resemblance to Crohn's disease (Hancock, 1958) with prominent cobblestoning and pseudopolyposis. The characteristic girdle ulcer spanning the circumference and resulting in a sharply outlined stricture, while still the most common presentation in the ulcerative variety, may not always be present. In the series of Hoon et al (1950), they were present in only four out of the 22 cases of the ulcerative type.

After our experience with a large series it is admitted that a clear distinction may sometimes be difficult, especially on macroscopic observations alone, but certain features help to make such a distinction. These are listed in the Table. None of the distinguishing features except caseation in the granulomas are absolute but a careful examination of the specimen and an overall consideration of the above features will help to distinguish most cases.

Granulomas are a feature common to both the diseases. It is not unusual to find them in the mesenteric lymph nodes, while the bowel shows none in tuberculosis, whereas in Crohn's disease lymph nodes do not show granulomas, if none are seen in the intestine (Morson, personal communication). Caseation, which is considered an essential criterion in the diagnosis of tuberculosis, may often be difficult to demonstrate. Yet, there are several features which help to distinguish the non-caseating tuberculous granulomas from those of Crohn's disease, as indicated in the Table. Of special significance is their tendency to confluence in the former
(Figs. 5 and 6A), as also is emphasized by Howell and Knapton (1964) and Hawley et al (1968), which accounts for a greater variability in size and stage of evolution. In contrast, the granulomas in Crohn's disease remain discrete, even if lying adjacent to each other (Fig. 6B), and represent the same stage of evolution, as was also observed by Cornes and Stecher (1961). They too have a "punched-out" appearance, lacking a peripheral zone of inflammatory cell infiltration.

The cracks and fissures, emphasized by Lockhart-Mummery and Morson (1964), Williams (1964), and Morson (1968) as an important diagnostic feature for Crohn's disease, were specially looked for in all our cases. They have been observed in but a few cases of tuberculosis, especially of the hypertrophic variety, as angular or linear tears originating from the ulcerated surface, but were never seen to penetrate deeper than the muscularis propria (Fig. 7A), unlike Crohn's disease in which they extend deep, through the muscle coat almost up to the serosa (Fig. 7B).

Inflammation in both these conditions has a transmural spread, and penetrates through the muscle coat, although relatively less often in Crohn's disease. In the latter, it is seen mostly as a non-specific inflammatory infiltrate extending between the muscle planes on the serosa, whereas in tuberculosis it is comprised of characteristic granulomas.

**EFFECTS OF CHEMOTHERAPY**

The morphological pattern of healing responses under the influence of chemotherapy observed in proven cases of tuberculosis does not differ significantly from those described by Rappaport et al (1951) in Crohn's disease, or those which may occur spontaneously. Unlike the lung (Denst, 1953; Poppe de Figueirido and de Paola, 1955; Puzik and Uvavova, 1959), there are no specific morphological features which are associated with the tissue healing under such a regimen. It is notable that although granulomas had disappeared from the intestinal lesions, some of them continued to show ulceration, at least in parts. Whether the ulcers continue to be perpetuated due to secondary infection by other organisms or to some other factors is not understood. It is possible that it may represent recurrent ulceration due to factors other than tuberculosis. It is also interesting that no evidence of healed granulomas was seen in the intestines, although the mesenteric lymph nodes did show a progressive hyalinization of such lesions.

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