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Axel von Herbay · Matthias Maiwald
Hans-Jürgen Ditton · Herwart F. Otto

Histology of intestinal Whipple's disease revisited

A study of 48 patients

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Abstract Whipple's disease is an infectious disorder with intestinal and extra-intestinal manifestations. We reinvestigated the intestinal histology in a series of 48 patients (10 females, 38 males; mean age 56.5 years, standard deviation of the mean ± 11.2 years). A total of 126 biopsy samples, obtained prior to, during, and after therapy, were evaluated by light microscopy. In 43 patients (90%), histology was consistent with common descriptions, while it was uncommon in 3 patients (6%), and non-diagnostic in 2 patients (4%). During treatment, several alterations occurred. Apart from a continuous decrease in PAS-positive macrophages, the pattern of mucosal infiltration changed from diffuse to patchy. Moreover, the cytological aspects of PAS-positive macrophages changed substantially, and this change was used to propose four different subtypes. Initially, subtype 1 macrophages predominated (74%), but showed a gradual decrease within a few months of therapy. After 15 months, subtype 3 and subtype 4 macrophages predominated (< 80%). In 7 of 9 patients followed over long periods some subtype 3 or subtype 4 macrophages persisted. It is concluded that at diagnosis and during treatment the intestinal histology of Whipple's disease is heterogeneous. A few PAS-positive macrophages commonly persist at long-term follow-up. This and other features suggest the presence of a persistent immune defect.

Key words Whipple's disease · *Tropheryma whippelii* · SPC cells · Pathology · Endoscopy

Dedicated to Prof. Dr. med. Gerhard Seifert, Emeritus Director of the Institute of Pathology, University of Hamburg, Germany, on the occasion of his 75th birthday

A. von Herbay (✉) · H. F. Otto
Institute of Pathology, University of Heidelberg,
Im Neuenheimer Feld 220, D-69120 Heidelberg, Germany
Tel.: (49) 6221 56 26 75, Fax: (49) 6221 56 52 51,
e-mail: Axel_von_Herbay@krzmail.krz.uni-heidelberg.de

M. Maiwald · H.-J. Ditton
Institute of Hygiene and Medical Microbiology,
University of Heidelberg, Heidelberg, Germany

Introduction

Whipple's disease is an infectious disorder with intestinal and extra-intestinal manifestations [30]. As the causative gram-positive rod-shaped bacterium, *Tropheryma whippelii* [22, 31], cannot be cultured, the diagnosis of Whipple's disease generally relies on histology. With approximately 700 cases reported [3], the histology of the intestinal mucosa in Whipple's disease may be assumed to be well characterised. However, descriptions of histology in previous case reports and clinical series were relatively short [10, 12, 14, 18]. To date, there is only one histopathological study, of 16 patients with short-term follow-up [8, 12].

The histological hallmark of Whipple's disease are macrophages with characteristic periodic acid-Schiff (PAS)-reagent positive granular or sickle-form particles in the cytoplasm. (In diagnostic pathology, the term sickle-form particle-containing cells, or SPC cells [26], has become a common term for all PAS-positive macrophages in Whipple's disease.) Even months after a patient has entered clinical remission, PAS-positive macrophages may still be present, and this finding can cause diagnostic uncertainty. Furthermore, other bacterial infections in AIDS patients may mimic the histology of Whipple's disease with the presence of PAS-positive macrophages [13, 25, 29].

As the specific macrophages of Whipple's disease warrant more detailed examination, we took a new look at the histology of the intestinal mucosa in a fairly large series of patients with Whipple's disease who were followed up for up to 12 years. The first aim was to emphasize the variability of histological findings, which includes some uncommon variants of the common textbook histology. The second aim was to characterise the course of mucosal histology, including changes the PAS-positive macrophages, at the time of diagnosis, during

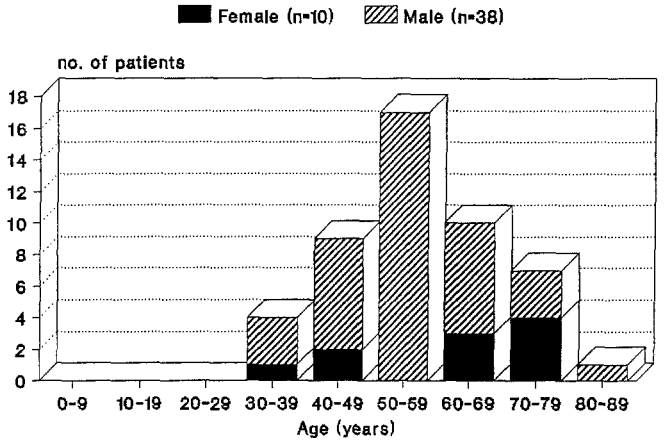


Fig. 1 Distribution of age and sex among the 48 patients in the study group

treatment and thereafter, in order to provide hints for the clinical management of patients.

Material and methods

A total of 126 small intestinal biopsies from 48 individual patients with Whipple's disease were examined; all 48 patients were diagnosed from 1983 through May 1996. Demographic data of the study group are summarised in Fig. 1. Biopsies of 11 patients were retrieved from the diagnostic archives of the Institute of Pathology, University of Heidelberg, and biopsies of 37 patients were sent for consultation (see Acknowledgements).

Intestinal biopsies from 47 patients were obtained by endoscopy, while intestinal tissue from 1 patient was obtained at autopsy. For the time before therapy, biopsies were available from 44 patients. A total of 82 follow-up biopsies was available from 34 patients. The latter samples were obtained at various times during and after therapy (range: 1–140 months; median: 20 months: mean: 29.8 months, SD: 29.9 months).

The diagnosis of Whipple's disease in all 48 patients was based on the histological finding of SPC cells (see Results). Electron microscopy was performed with samples from 12 patients, and the presence of typical rod-shaped Whipple bacteria was documented. Polymerase chain reaction (PCR) analysis was applicated to intestinal biopsies from 44 patients at various times in the course of the disease. A specific DNA fragment of *Tropheryma whippelii* was detected in all 34 patients from whom adequate biopsies from the time before therapy were available. PCR results were reported elsewhere in detail [15].

All tissues were formalin-fixed or Bouin-fixed, processed, and embedded in paraffin by using standard histological techniques. Stains were performed using haematoxylin-eosin, and periodic acid Schiff (PAS) reagent, without and with prior diastase digestion.

All intestinal biopsies were examined by light microscopy for a number of histological features. These included seven main items, which are summarised in Table 1. Examination of the follow-up biopsies during antibiotic treatment focused on the number of infiltrating PAS-positive macrophages (item 3, Table 1) and on the localisation of PAS-positive macrophages (item 4, Table 1). In addition, special attention was given to the cytological aspects of PAS-positive macrophages. For further characterisation of differences among them, it seemed appropriate to define several subtypes (see Results). The relative percentages of these subtypes among all PAS-positive macrophages present in a biopsy sample were estimated semi-quantitatively.

Information on the gross findings at first endoscopy was available from 21 patients and was correlated with the histological findings.

Results

Findings at diagnosis

In 43 of the 48 patients (90%), intestinal histology was consistent with conventional descriptions in textbooks, while in 3 patients (6%) histology was unconventional but diagnostic. In 2 patients (4%), however, intestinal histology was not diagnostic of Whipple's disease.

In the biopsies of the 43 patients showing typical changes, the mucosal stroma was infiltrated by numbers of macrophages with PAS-positive, diastase-resistant granular particles in the cytoplasm (Fig. 2). Apart from

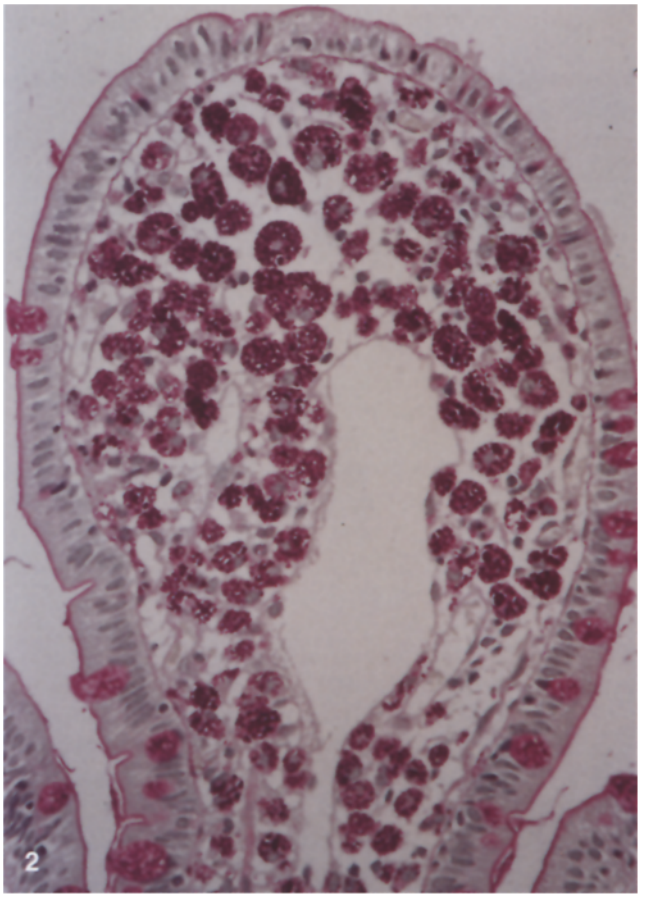
Fig. 2 Common histology of Whipple's disease. Very numerous macrophages with intensely PAS-positive, coarsely granular particles in the cytoplasm infiltrating the intestinal mucosa. PAS stain ▶

Fig. 3a–c Uncommon histologies of Whipple's disease. **a** Submucosal variant, characterised by numerous macrophages with coarsely granular, intensely PAS-positive particles in the cytoplasm, which are exlusively present in the submucosa. **b, c** Epithelioid granuloma in the duodenal mucosa, in addition to several PAS-positive macrophages (**b** hemalaun-eosin, **c** PAS)

Table 1 Histological features examined in the 126 biopsy samples from 48 patients

Item no.	Histological feature	Criteria, measurement
1	Shape of villi Height of villi, length of crypts	Finger-like or clubbed villi Ratio, determined by an ocular micrometer
2	Pattern of mucosal infiltration by PAS+ macrophages	Diffuse or patchy
3	Number of PAS+ macrophages	Semi-quantitative scores[a]: 0, 1+ to 4+
4	Localization of PAS+ macrophages	Semi-quantitative estimates in n×10% for: villi or upper mucosa, pericryptal or basal mucosa, and submucosa
5	Presence of lipid deposits and/or lymphangiectasia	Semi-quantitative scores[a]: 0, 1+ to 4+
6	Numbers of neutrophilic and eosinophilic granulocytes	Semi-quantitative scores[a]: 0, 1+ to 4+
7	Other histological findings	e.g. *Giardia lamblia*

[a] Semi-quantitative scores: 0, none; 1+, few; 2+, several; 3+, numerous; 4+, very numerous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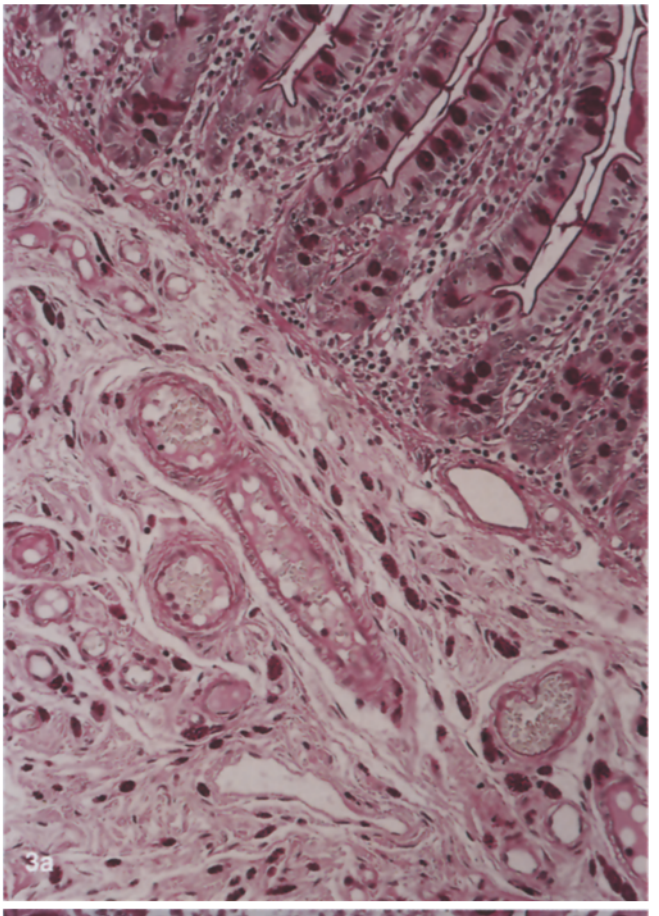
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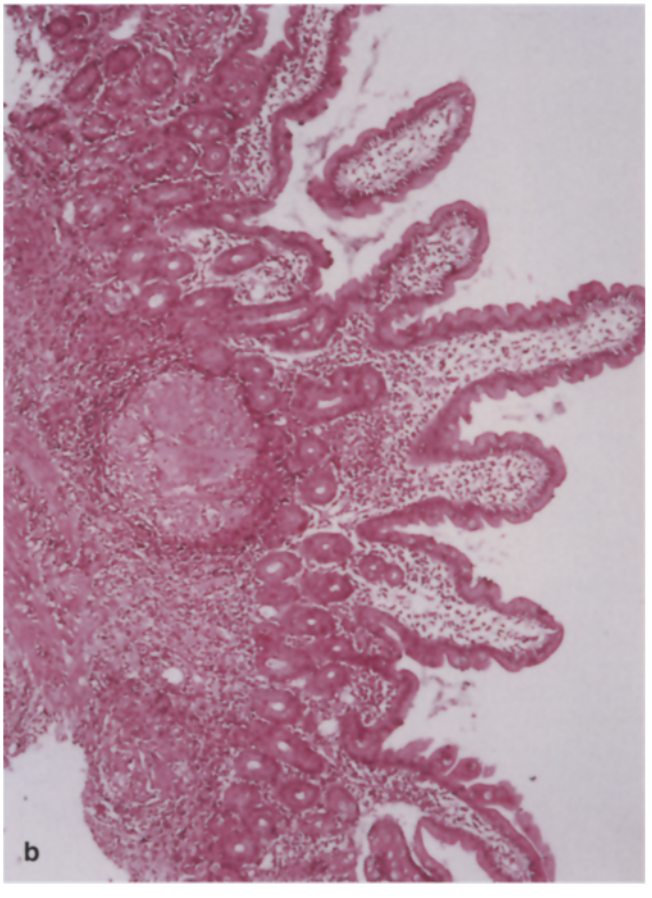
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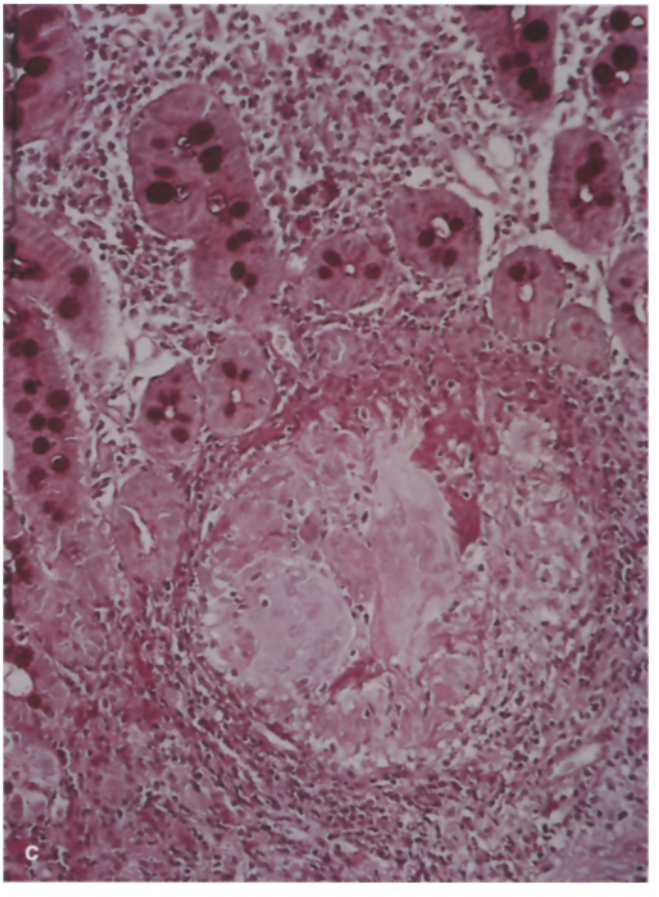
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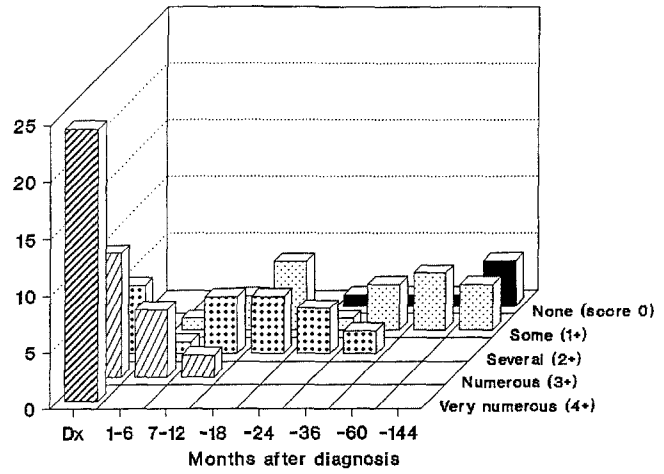

Fig. 4 Numbers of PAS-positive macrophages at the time of diagnosis (*Dx*) and at intervals therafter (in months), as estimated semi-quantitatively by scores 1+ to 4+ in 30 patients. Within a few months of treatment there is a substantial decrease of PAS-positive macrophages, but some cells may persist even after many years

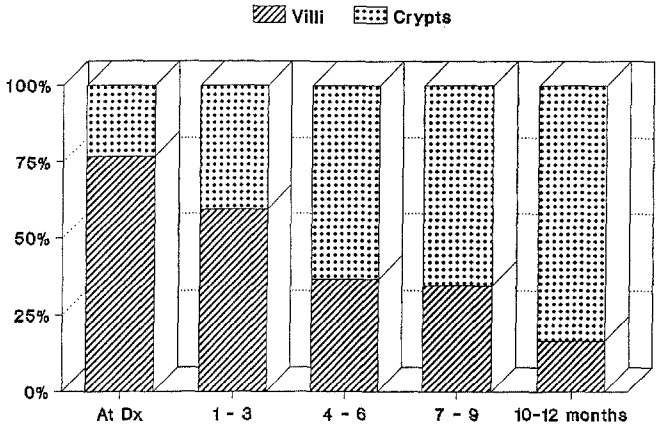

Fig. 5 Intramucosal sites of PAS-positive macrophages, estimated semi-quantitatively as relative percentages in the interstitium of either villi or crypts. After diagnosis (*Dx*) and start of treatment, there is a continuous shift from the upper to the lower part of the mucosa

this consistent finding, there were several other aspects that differed among the patients. First, the mucosal structure was abnormal, featuring clubbed villi, in 34 patients (79%). In the remaining 9 patients (20%), the mucosal structure was relatively normal with finger-shaped villi. The mean ratio of villi to crypts was 2.33 (SD ± 0.67). Secondly, the pattern of infiltration by PAS-positive macrophages was diffuse in 29 patients (67%), but patchy in 14 patients (33%). Thirdly, the number of infiltrating PAS-positive macrophages was markedly variable, estimated by the score of 4+ in 25 patients, score 3+ in 11 patients, score 2+ in 6 patients, and score 1+ in none of the patients. Fourthly, intramucosal lipid deposits were present in 76% of the patients (in various amounts) but absent in 24%.

Three patients had uncommon histological variants, which were nevertheless diagnostic. In 2 patients, PAS-positive macrophages were present but were essentially confined to the submucosa, while the mucosal structure was normal and lipid deposits were absent (Fig. 3A). In 1 further patient, PAS-positive macrophages were present in the mucosa but in addition, a large epithelioid granuloma had been formed in the mucosa (Fig. 3B).

Intestinal biopsies of 2 patients were not diagnostic of Whipple's disease, as no PAS-positive macrophages were visible. The diagnosis of 1 patient had previously been established by brain biopsy. Duodenoscopy was performed after 1 week of antibiotic treatment. The gross findings at endoscopy were reported to be normal, and only a single biopsy specimen was taken as a sample. In the other patient, small intestinal biopsies were obtained 2 years before the histological diagnosis of Whipple's disease, which was then established by abdominal lymph node biopsy.

In the majority of patients, PAS-positive macrophages were apparently the only leucocytes infiltrating the intestinal mucosa, despite the invasion by large numbers of

Fig. 6a–d Histological subtypes of PAS-positive macrophages in Whipple's disease: **a** subtype 1, **b** subtype 2, **c** subtype 3, **d** subtype 4 macrophages ▶

Table 2 Proposed subtypes of PAS-positive macrophages in Whipple's disease

Subtype	Light microscopy: cytological characteristics	Electron microscopy
1	Only or mostly coarse granular cytoplasmic inclusions, intensely PAS positive (SPC cells)	Lysosomes filled with numerous rod-shaped bacteria, with only minor degradation. Ultrastructural characteristics of *T. whippelii* can be recognized
2	Some coarse granular inclusions, intensely PAS positive. Background of diffuse or fine granular, more faintly PAS-positive cytoplasm	Lysosomes filled with bacteria showing evidence of partial degradation: Identification of bacterial shape and size may be possible, but not of cell wall details
3	No granular inclusions, only diffuse and faintly PAS-positive material in the cytoplasm	Lysosomes filled with bacterial cell wall remnants. No intact bacteria. Bacterial identification not possible
4	Foamy cytoplasm, minimal or no PAS-stain affinity at all	Not determined

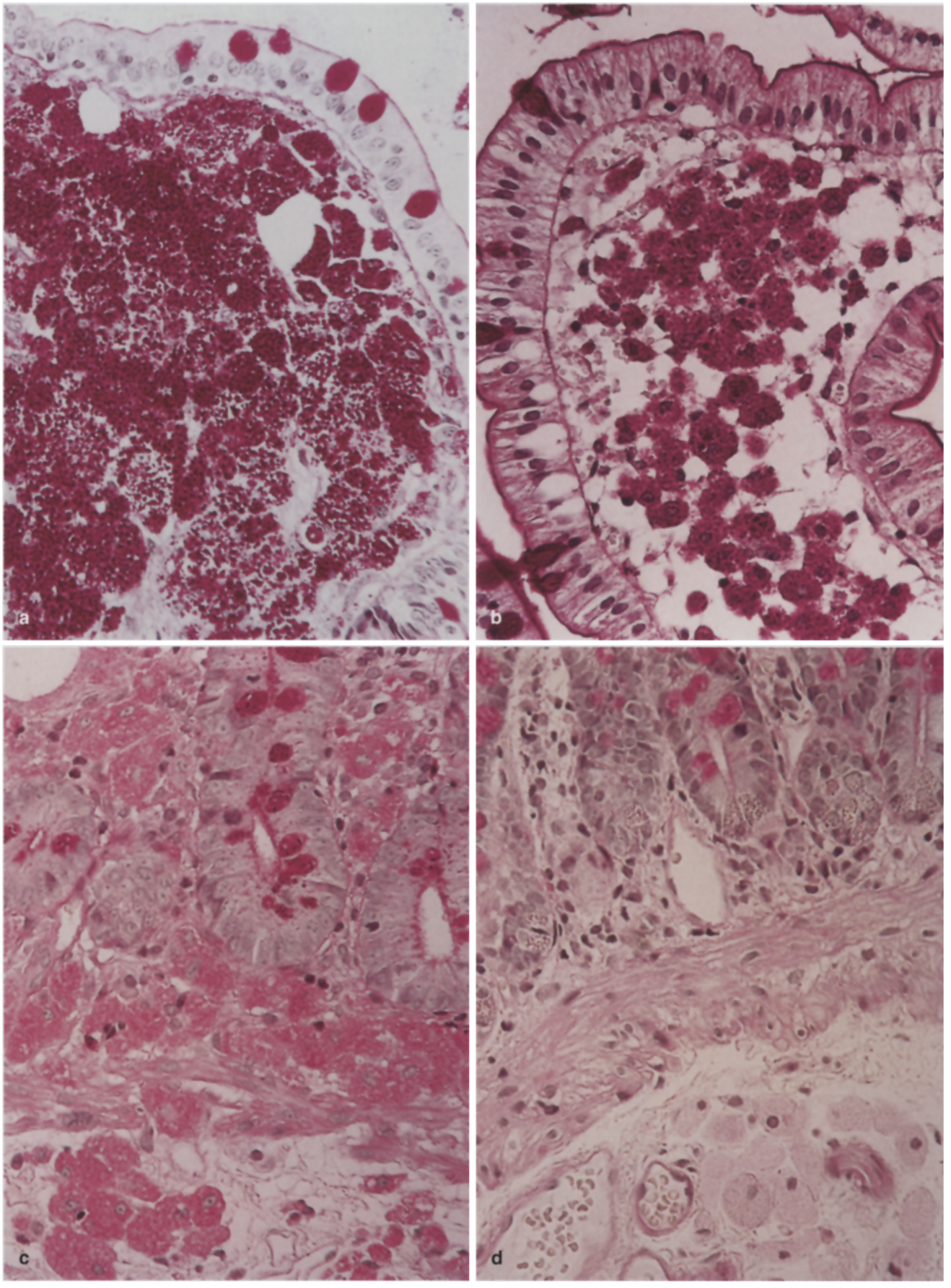
a
b
c
d

Fig. 7 Ultrastructure of subtype 3 macrophages (same patient as in Fig. 6C). After 22 months of treatment, only filamentous remnants of bacteria are present within large phagolysosomes

bacteria. Only in 31% of patients were a few or moderate numbers of neutrophilic granulocytes associated with the macrophages; they were absent in the remaining patients. Eosinophilic granulocytes, however, were somewhat more frequently present: there were a few or moderate numbers associated with the macrophages in 58% of the patients.

In the biopsies of 4 patients, histological evidence for Whipple's disease was associated with concurrent infections. In all 4 of these patients, unequivocal trophozoites of *Giardia lamblia* were adjacent to the villous surface. In only two of the diagnostic reports of these patients was this coinfection mentioned; in both of the other cases, *Giardia lamblia* was recognised during our retrospective examination. Apart from *Giardia lamblia*, no other pathogens were recognised by light microscopy.

Among the 21 patients for whom data information on findings at the first endoscopy were available, white or yellow plaques in the intestinal mucosa were reported in 15. In the biopsy samples from 13 of these 15 patients, lipid deposits or lymphangiectasia were present, while they were not documented in the biopsies of the other 2 patients. In contrast, the endoscopic appearance was reported as grossly normal in six patients, and histology revealed neither lipid deposits nor lymphangiectasia in the respective biopsies.

Findings during and after treatment

During and after treatment, the histopathological lesions improved in all 34 patients who were followed up. This improvement was relatively uniform in 32 of the 34 patients, and was achieved within 12 months of treatment. After 24 months, only minor lesions still persisted. In 2 patients, however, regression was markedly different and is described later.

Reversal of the mucosal structure to normal occurred early after the initiation of treatment. Within 1–12 months of treatment, previously clubbed villi became finger-like in 17 of 21 patients who were followed up, with a median of 9 months to normalisation. The ratio of villi to crypts improved within 3 months (mean ratio 2.7, SD ± 0.7), and returned to normal after 12 months (mean ratio 3.1, SD ± 0.4). Mucosal lipid deposits disappeared within 8 months of treatment and were not observed in biopsies obtained thereafter. In 1 patient, lymphangiectasia persisted for 1 year.

During remission, several different aspects concerning the number, distribution, and the morphology of PAS-positive macrophages were noted. First, the number of PAS- positive macrophages decreased in all patients, albeit with wide individual variation (Fig. 4). This regression occurred stepwise, with a gradual decrease of the number of macrophages in consecutive biopsy samples, which seemed proportional to the individual load of PAS-positive macrophages at the beginning of antibiotic treatment. Secondly, the pattern of mucosal infiltration by PAS-positive macrophages changed from diffuse to patchy within 3–30 months. With the exception of 2 patients (see below), resolution of diffuse infiltrates of macrophages was observed after a median of 9 months. Thirdly, there was a shift in the localisation of PAS-positive macrophages (Fig. 5). At the time of diagnosis and in the first 3 months of treatment, the majority of macrophages was present in the interstitium of villi. Later on, the majority of macrophages was localised in the pericryptal interstitium. Only in some patients was submucosal tissue obtained, and in these patients less than 10% of macrophages were localised in the submucosa. Fourthly, there were substantial alterations in the cytological aspects of PAS-positive macrophages. These cytological features showed four different variants distinguishable by light microscopy. Therefore, it seems appropriate to propose four subtypes of PAS-positive macrophages in Whipple's disease (Table 2; Figs. 6, 7).

At the time of diagnosis, the vast majority (74%) of PAS-positive macrophages were of subtype 1, with granular and sickle-form particles in the cytoplasm, while other subtypes were rarely present (classical SPC cells; Fig. 8). During treatment, the composition of macro-

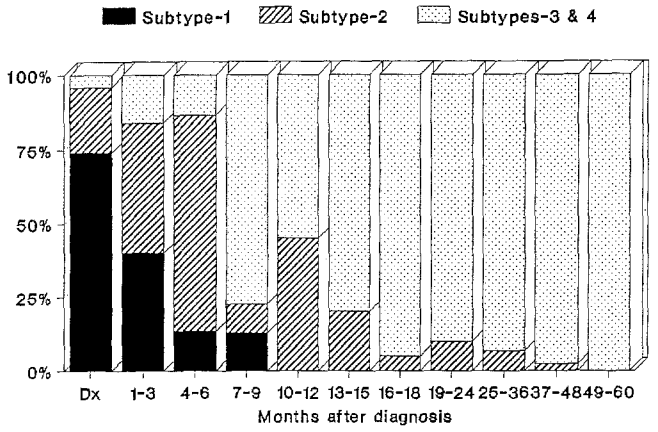

Fig. 8 Composition of PAS-positive macrophages with regard to the subtypes, given as estimated relative percentages. After diagnosis (*Dx*) and start of treatment, the classic SPC (subtype 1) cells soon disappear, while macrophages with other PAS staining patterns subtypes 2 or 3) may persist for years

phage subtypes changed dramatically (Fig. 8). Within 3 months of treatment, the mean percentage of subtype 1 macrophages, or SPC cells, decreased to less than half (40%) of all PAS-positive macrophages. After 6 months of treatment, subtype 1 macrophages represented only a small minority (13%). After 10 months or more, subtype 1 macrophages were absent. Correspondingly, the number of subtype 2 macrophages increased shortly after the start of treatment (22% at diagnosis), with a peak at 6 months (76%), and decreased thereafter. After more than 1 year, subtype 2 macrophages persisted for up to 4 years as a small minority. The proportion of subtype 3 macrophages increased continuously from the beginning of treatment (4% at diagnosis, 13% after 6 months). After 1 year, they represented the majority (>80%) of PAS-positive macrophages that were still present (Fig. 8). Subtype 4 macrophages were observed in 5 patients, occurring within a range of 2–12 years.

In 2 patients, the response to treatment was obviously different from that in the other 32 patients. In 1 female patient, with the maximum number of PAS-positive macrophages at the time of diagnosis in this series, a continuous regression of histology was documented during treatment, but it was slower than in the other patients. Even after 2 years, numerous (score 3+) PAS-positive subtype 3 macrophages persisted in the mucosa and submucosa. In 1 male patient, only minor regression was observed despite continuous antibiotic treatment. In this patient, subtype 1 macrophages persisted until his last follow-up examination at 26 months.

From 9 individual patients, a total of 13 intestinal biopsies were obtained 5 years or later after the diagnosis. In 7 of the 9 patients, some PAS-positive subtype 3 or subtype 4 macrophages were still present, even after 12 years. These cells were localised either in the basal mucosa, or in the submucosa. Only in 2 of the 9 patients followed long term were no residual PAS-positive macrophages recognised.

Discussion

This series confirms the histological features of intestinal Whipple's disease which have been described previously in case reports (for review see [3]) and in some series [8–10, 14, 18]. In addition, this larger series describes some heterogeneity of mucosal histopathology, which includes two uncommon variants. Moreover, new information has been gained concerning the changes of histological lesions during and after therapy.

At the time of diagnosis, the common histology is characterised by mucosal infiltration by PAS-positive macrophages, but also by various other lesions. The common immune response consists rather exclusively in this infiltration by macrophages, while the formation of granulomas is an uncommon variant [1, 2]. Other mononuclear leucocytes, including plasma cells [8], as well as eosinophilic and neutrophilic granulocytes, are either not increased in numbers, or are rare or absent. This cellular composition is clearly uncommon with respect to the presence of bacterial invasion in the intestinal mucosa, and this response is suggestive of a defective mobilisation and chemotaxis of other leucocytes towards the site of infection.

During treatment, the mucosal histology reverts towards normal within several months, but with a protracted decrease of PAS-positive macrophages. Although the disappearance of extracellular bacteria, and the regression of intracellular bacteria was emphasised in several ultrastructural studies [5–7, 28], the practical impact of a corresponding regression that can be assessed at the histological level was not appreciated. Traditionally, histopathologists equated all PAS-positive macrophages in Whipple's disease with SPC cells [26]. However, classical SPC cells, or subtype 1 macrophages, as proposed in this paper (Table 2), disappear within 10 months of treatment, and then the vast majority of PAS-positive cells are subtype 3 macrophages. These do not contain intact bacteria, and no DNA of *Tropheryma whippelii* can be detected [15]. The prolonged intracellular presence of incompletely digested remnants of bacteria is suggestive of defective macrophage function, perhaps owing to lack of activation.

Long term, the common persistence of some PAS-positive macrophages in patients with complete clinical remission is another intriguing finding [12, 20]. These persistent PAS-positive macrophages are the subtype 3 or subtype 4 macrophages proposed here. This feature suggests that this is a morphological correlate of a persistent defect of macrophages.

At any time the histological findings are suggestive of an impaired immune response, the features of which are consistent with a defect in the complement system of immunity [24]. Evidence for such a defect in Whipple's disease was recently provided by immunological studies in a series of 27 patients [19]. Prior to, during, and for many years after treatment, there was a persistent reduction of mononuclear cells in the peripheral blood expressing the α-chain of complement receptor 3 (CD11b)

[19]. There was no reduction of those mononuclear cells, which usually express CD11b, that is monocytes (CD14+), and natural killer cells (CD56+) [19]. The decrease of complement receptor 3 (CR3) may indicate functional impairment of the complement system in patients with Whipple's disease.

Further evidence, albeit indirect, for impaired immunity in Whipple's disease is provided by the association of Whipple's disease with various other infections. This association has been noted in several cases reported during the past 10 years (for review see [21]), and the present series adds some new cases. Together, these observations challenge the previous reasoning, which emphatically denied that Whipple's disease patients are more likely to develop other infections, as few such patients had been reported in the literature [3]. For instance, among the 696 patients evaluated, only three cases were associated with *Giardia lamblia* infection [3]. In contrast, among the 48 patients in this series alone, 4 cases of giardiasis were diagnosed. In our series, 2 of the 4 cases with giardiasis were not mentioned in the original diagnostic reports.

Heterogeneity of intestinal histology also includes a submucosal variant of Whipple's disease. In 2 of our 48 patients (4%) PAS-positive macrophages were found exclusively in the submucosa. This finding was reported only in two previous autopsy cases, and the uncommon presentation was attributed to previous antibiotic treatment [17, 27]. Although at least 1 of our 2 patients was also pretreated with antibiotics, it seems important to note that biopsies from both our patients included numerous subtype 1 macrophages. As this finding did not reappear in any of 82 follow-up biopsies were studied, it has to be questioned whether the submucosal variant of Whipple's disease is really a consequence of antibiotic treatment. Alternatively, in these rare patients the route of intestinal infection may have been different from that in the majority.

Heterogeneity of intestinal morphology is not limited to histology. In this series, approximately 1 in 4 patients did not present with characteristic gross lesions at endoscopy [12, 23]. Previously, the white and yellow plaques seen at endoscopy were considered to reflect the mucosal infiltration by numbers of macrophages [11], the clubbing of villi [12], or lymphangiectasia [23]. Our present data now provide evidence that the white and yellow plaques seen at endoscopy are most frequently due to lipid deposits. Similar endoscopic lesions are seen in some rare primary disorders of intestinal lipid metabolism, such as abetalipoproteinaemia and hypobetalipoproteinaemia [4].

The data recorded in this paper may give some hints for clinical practice whenever Whipple's disease is suspected or diagnosed. First, as there are definitely some patients without characteristic endocopic findings, a normal duodenoscopic appearance should not prompt the investigator to reduce the number of biopsies being taken. In view of the frequency of patchy lesions, five biopsies should always be taken at the time of diagnosis and thereafter, to minimise possible sampling errors. Secondly, considering the common time course of histological regression, follow-up biopsies are most informative when obtained after 10–12 months of treatment. At this time, a significant histological improvement should be achieved, as was reported in a previous series [12] and as seen in 94% of our patients.

The significance of PAS-positive macrophages found during follow-up will vary according to the subtypes present. In those of our patients diagnosed and followed by PCR analysis of intestinal biopsies, the conversion of PCR results from positive to negative occurred earlier than did histological remission [15] when the traditional view was respected that the presence of PAS-positive macrophages virtually rules out a histological diagnosis of definite remission in Whipple's disease. However, when the subtypes of PAS-positive macrophages proposed herein are evaluated, pairwise comparison of histology with PCR results [15] reveals that all PAS-positive subtype 3 macrophage infiltrates are PCR negative for DNA of *Tropheryma whippelii*.

In a practical context, the persistence of minor histological lesions for 24 months appears not to be of clinical relevance. At this time, only small numbers of PAS-positive subtype 3 macrophages are present, which are found to lack intact bacteria when examined by electron microscopy and to lack DNA of *Tropheryma whippelii* when PCR is performed [15]. In addition, as negative intestinal histology and negative intestinal PCR do not preclude extra-intestinal manifestations [15], further endoscopic and histological follow-up appears not to be helpful when performed more than 2 years after diagnosis.

When the intestinal histology is considered with an eye to possible prognostic factors, this series does not provide conclusive information. Among the 34 patients followed up, 1 did not enter clinical remission of intestinal disease, and 4 others with intestinal remission developed symptomatic cerebral Whipple's disease [16]. Among these 5 patients, regression of histology took the most usual course in 3 patients, and was different in the other 2 (reported separately above). To recognise patients at risk for cerebral relapse, diagnostic examination of cerebrospinal fluid by cytology and polymerase chain reaction analysis appears to be more appropriate [16].

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