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CASE REPORT

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Generalized AA-amyloidosis in a 58-year-old Caucasian woman with an 18-month history of gastrointestinal tuberculosis

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Abstract We report on a 58-year-old Caucasian woman who went to a general practitioner about recurrent abdominal pain, night sweats and weight loss of a few weeks' duration. Once gynaecological disease had been ruled out, the patient was admitted to hospital with severe abdominal pain and intestinal obstruction and a right-sided hemicolectomy was performed. Following the investigation of osteolytic lumbar vertebrae, 18 months after visiting the general practitioner the patient was finally found to be suffering from generalized AA-amyloidosis secondary to gastrointestinal tuberculosis. This had been misinterpreted as Crohn's disease. Re-examination of the specimens from the right-sided hemicolectomy demonstrated that scanty deposits of AA-amyloid were present 9 months after the first presentation. AA-amyloid can thus be present in serious inflammatory disease even during the first 9 months after the initial clinical presentation.

Key words Amyloid · Gastrointestinal tuberculosis · *Mycobacterium bovis* · Crohn's disease

Introduction

The acute phase protein serum amyloid A (SAA) is the precursor of the AA-fibril protein deposited in AA-amyloidosis. The latter is commonly associated with chronic inflammatory disease and is characterized by fibrillar protein deposits with specific tinctorial and structural properties [11, 12, 19, 31]. Depending on the pattern and progress of deposition, severe and even lethal complications may arise [11, 12]. Among the causes of AA-amyloidosis are rheumatic diseases (ankylosing spondylitis and rheumatoid and juvenile arthritis); idiopathic diseases (Crohn's disease and ulcerative colitis); inherited diseases (such as familial Mediterranean fever); and infectious diseases (tuberculosis and leprosy) [12]. The absolute and relative prevalence of the individual diseases associated with AA-amyloidosis shows significant geographical and temporal differences. Until the middle of this century tuberculosis was among the most common causes of AA-amyloidosis in the West [2]. During the second half of this century, the incidence of tuberculosis has decreased, leaving chronic rheumatic and idiopathic inflammatory diseases as the leading causes of AA-amyloidosis in the Western world [17, 27, 34, 36]. The incidence of secondary AA-amyloidosis among patients who suffer from tuberculosis is approximately 2% [36]. The prevalence of AA-amyloidosis among persons affected by ankylosing spondylitis, rheumatoid arthritis and Crohn's disease ranges from 0.5% to 13% [10, 12, 15, 16, 26, 29]. However, in the Third World and on the Indian subcontinent, chronic infectious diseases such as tuberculosis and leprosy remain the major causes of AA-amyloidosis [5, 12, 21, 28, 30]. In India, tuberculosis of various organs accounts for 59.1% of AA-amyloidosis [5].

Irrespective of the underlying disease, the general opinion is that AA-amyloidosis occurs after a long period of an ongoing inflammatory and infectious process. The time lapse ranges from 1 to 37 years, with means of 6.9 and 24.1 years after the initial diagnosis of a chronic rheumatic or infectious disease [5, 12, 15, 29]. Accordingly, amyloidosis is rarely suspected in the early course of a possibly chronic or recurrent inflammatory disease. We report here the history of a 58-year-old Caucasian woman who had histologically proven gastrointestinal deposits of AA-amyloid 9 months after the onset of clinically symptomatic gastrointestinal tuberculosis. As the disease progressed it was inadequately treated, and 18 months after her initial presentation histological evi-

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Table 1 Summary of the clinical history of a 58-year-old Caucasian woman with gastrointestinal tuberculosis and generalized AA-Amyloidosis

Date	Clinical history	Histological proof of amyloid
Autumn 1996	The patient attends the general practitioner (GP) because of night sweats, abdominal pain and weight loss of a few weeks duration; GP referral to gynaecologist ruled out a gynaecological disease	
May 1997	Admission to a general hospital with persistent abdominal pain and swelling of inguinal lymph nodes	
	Lymph node biopsy reveals centrally necrotizing epithelioid granulomas, and the first histopathology report states tuberculosis as a differential diagnosis	No amyloid[a]
	Persistent pain and intestinal obstruction requiring right-sided hemicolectomy: the second histopathology report describes epithelioid granulomas and states the diagnosis of Crohn's disease	Sparse vascular deposits of AA-amyloid in the intestinal submucosa and subserosa[a]
December 1997	Referral to a specialist chest clinic for the investigation of tuberculosis ruled out pulmonary tuberculosis: chest X-ray, CT scan of the chest and pulmonary function test within normal limits, Tine test negative	
January 1998	Referral to orthopaedic clinic of the University Hospital for investigation of severe back pain: diagnostic excision from the 4th and 5th lumbar vertebrae necessary owing to osteolytic changes. Histopathology report describes necrosis and epithelioid granulomas with a low count of inflammatory cells, still highly suggestive of tuberculosis	Small vascular deposits of AA-amyloid[a]
	Liver biopsy	Vascular AA-amyloid in portal vessels
February1998	Referral to the Department of Gastroenterology, Hepatology and Infectious Diseases of the University Hospital for case review: final diagnosis of gastrointestinal tuberculosis (see text)	
	Biopsies from the ileocolonic anastomosis and large intestine	Large amounts of vascular and interstitial AA-amyloid deposits

[a] The presence of amyloid was investigated retrospectively

dence of generalized AA-amyloidosis with proteinuria was evident.

Clinical history

After visiting her general practitioner (GP) 18 months previously with symptoms of recurrent abdominal pain, night sweats and weight loss of few weeks' duration, a 58-year-old Caucasian woman was referred to the Department of Gastroenterology, Hepatology and Infectious Diseases of the University Hospital for review. The past medical history of the patient included uncomplicated deliveries of two children, no abortions or miscarriages, and spontaneous passage of a kidney stone. The family and social history gave no evidence of exposure to tuberculosis, and the patient was taking no regular medication. Following the initial presentation, the GP referred the patient to a gynaecologist, who excluded gynaecological disease. The symptoms continued to occur intermittently, and the patient was finally admitted to a general hospital. Biopsy of enlarged inguinal lymph nodes showed necrotizing epithelioid granulomas, and in the first histopathology report tuberculosis was mentioned as a differential diagnosis. The tuberculin test was positive at this time, but the patient was assumed to have been vaccinated, so that the test was interpreted as unreliable. Subsequently, a right-sided hemicolectomy was necessary because the patient was complaining of severe abdominal pain and intestinal obstruction. The second histopathology report described epithelioid granulomas in the ileocolonic segment resected, and a diagnosis of Crohn's disease was made. Treatment was started with oral steroids and mesalazin. In addition, the patient was referred to a specialist chest clinic, where clinical examinations, chest X-ray, CT scan of the chest, pulmonary function tests and Tine test revealed no evidence of pulmonary tuberculosis. A year after the initial presentation the patient was suffering from back pain; a CT scan of the spine revealed osteolytic changes to the 4th and 5th lumbar vertebrae, and diagnostic excision was deemed necessary. Examination of the surgical specimens obtained demonstrated necrotizing epithelioid granulomas, and the third histopathology report again stated tuberculosis as a differential diagnosis. During investigation of the patient for a malignant neoplastic disease – there had been a total weight loss of 20 kg since the onset of her clinical symptoms – ultrasound of the abdomen showed enlarged peripancreatic and para-aortic lymph nodes, and also several liver lesions measuring approximately 12–22 mm. Liver biopsies were performed for histopathological examination (see below). Subsequently, the patient was referred to the Department of Gastroenterology, Hepatology and Infectious Diseases of the University Hospital for review. (The clinical course after the initial presentation is summarized in Table 1.) The patient had not so far received any tuberculostatic treatment.

On admission the patient was mobile, orientated in time, place and person, afebrile and normotonic, but cachectic, with 42 kg body weight to a height of 173 cm. The abdomen was not tender and the liver was slightly enlarged. Except for sensorineural deafness, no neurological deficiencies were evident. Laboratory investigations showed a normocytic anaemia, with haemoglobin of 6.33 mmol/dl and PCV of 0.31 l/l, and lymphopenia (8% WCC). Alpha-2 globulin and C-reactive protein were elevated, the latter measuring 43 mg/l, with a normal ESR. Three weeks after the anti-inflammatory treatment was discontinued (see below) the ESR was 60 mm/h. Alanine aminotransferase (0.88 µmol/l) and lactate

dehydrogenase (10 µmol/l) were mildly elevated. Mild proteinuria of 0.63 g/24 h was found. Urea and electrolytes were within normal limits.

The ECG was normal. On chest X-ray only minimal pleural effusions were evident, with blunt costophrenic angles. However, in view of the history and the first and third pathological reports, gastrointestinal tuberculosis was suggested as the most likely diagnosis. Colonoscopy demonstrated a normal mucosal lining of the colon with no lesions or strictures. The ileocolonic anastomosis showed small ulcers and a free passage. The patient was reported to have a regular stool pattern. Biopsies were obtained from the ileocolonic anastomosis and six different sites of the colon (see below). Bronchoscopy showed a mild tracheobronchitis but no evidence of malignancy. A bronchial lavage did not yield acid-fast bacilli, nor were acid-fast bacilli detected in the sputum, gastric fluid, stool or urine. Blood culture was negative on three occasions. However, the polymerase chain reaction finally detected mycobacteria of the tuberculosis group in the gastric fluid, and *Mycobacterium bovis* was cultured from samples of the liver biopsy. Thus, the diagnosis of gastrointestinal tuberculosis was confirmed on clinical and histopathological grounds (see below). Anti-inflammatory treatment was discontinued and the patient was started on rifampicin, isoniazid, ethambutol and vitamin B6.

Materials and methods

Specimens taken from all available biopsy and resection materials of the patient were re-examined; those obtained from the lymph node biopsy and right sided hemicolectomy were kindly provided by the particular pathology departments involved. All samples had been fixed in formalin and embedded in paraffin. Deparaffinized sections were stained with haematoxylin and eosin. The presence of amyloid was demonstrated by the appearance of green birefringence from alkaline alcoholic Congo Red staining under polarized light [32]. Amyloid was classified immunohistochemically with antibodies directed against AA-amyloid (dilution 1:500; clone mc1), transthyretin (1:600; polyclonal), β2-microglobulin (1:2000; polyclonal), λ-light chain (1:7500; polyclonal), and κ-light chain (1:7500; polyclonal; all Dakopatts, Hamburg, Germany). Prior to immunostaining the specimens were pretreated with 10 mM EDTA (2×10 min, 450 W microwave oven; anti-transthyretin), 0.5 U/ml protease 1 (16 min; anti-λ and anti-κ-light chain) or 0.1% papain (8 min; anti-β2-microglobulin). Immunostaining with anti-AA-amyloid did not necessitate any specimen pretreatment. Immunoreaction was visualized with the avidin–biotin complex method applying a Vectastain ABC–alkaline phosphatase kit (anti-AA-amyloid, -transthyretin, -λ- and -κ-light chain; distributed by CAMON, Wiesbaden, Germany) or UltraTech HRP Streptavidin-Biotin Universal Detection System (anti-β2-microglobulin; Immunotech, Marseille, France). Neufuchsin and 3,3-diaminobenzidine-tetrahydrochloride, respectively, served as chromogens. The specimens were counterstained with haematoxylin. The specificity of immunostaining was controlled using specimens containing known classes of amyloid and by omitting the primary antibodies.

Pathological findings

The lymph node biopsy from May 1997 (first biopsy) showed large, confluent and centrally necrotizing epithelioid granulomas with multinucleated Langhans cells. Amyloid was not found in Congo red-stained paraffin sections.

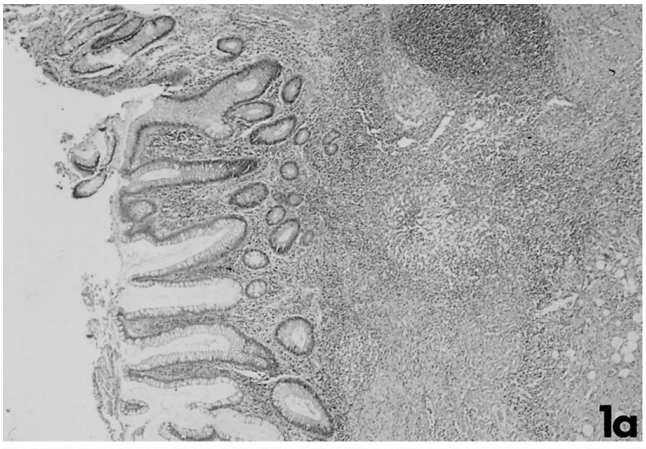
The specimens gained at the right-sided hemicolectomy from May 1997 (second specimen) showed ileic and colonic sections with a disproportionate inflammation. Large centrally necrotizing and occasionally confluent epithelioid granulomas were present in the mucosal, submucosal and subserosal layer as well as in the mesenteric lymph nodes (Fig. 1), separated by mildly inflamed or noninflamed segments. Occasionally the mucosa showed ulcers, and fibrosis of the muscularis propria was present. However, no mycobacteria were found with the Ziehl-Neelsen stain. The architecture of the crypts and the amount of goblet cells were preserved. The histopathological appearances were in keeping with a diagnosis of gastrointestinal tuberculosis rather than Crohn's disease. In Congo red-stained specimens scant deposits of amyloid were found in a few submucosal and subserosal vessels, without any significant thickening of the vessel walls (Fig. 2). The deposits immunoreacted with the antibody directed against AA-amyloid.

The specimens obtained from the 4th and 5th lumbar vertebrae in January 1998 (third specimen) also showed necrotizing inflammation with epithelioid granulomas. The granulomas showed a very low number of inflammatory cells, and very few multinucleated Langhans cells were found. Congo red staining revealed vascular amyloid deposits that were immunoreactive for AA-amyloid. The liver biopsy performed in the same month showed necrosis without any significant inflammatory infiltrate, and no evidence of a malignant tumour was found; AA-amyloid was present in portal vessels. The biopsy obtained from the ileocolonic anastomosis in February 1998 demonstrated an ulcerative lesion of the mucosa without centrally necrotizing granulomas. All six biopsies from the large intestine showed a regular mucosal architecture without any evidence of a chronic infectious or idiopathic inflammatory bowel disease. However, abundant vascular and interstitial AA-immunoreactive amyloid deposits were present, with marked thickening of the vessel walls and stenosis (Fig. 3). For this reason, the ulcerative lesion of the ileocolonic anastomosis was interpreted as ischaemic in nature. Since AA-amyloid deposits were present in the spine, liver and gastrointestinal tract, generalized AA-amyloidosis secondary to gastrointestinal tuberculosis was diagnosed.

None of the other antibodies (directed against transthyretin, λ- and κ-light chain and β2-microglobulin) immunostained any of the amyloid deposits present in the different biopsy specimens of this case.

Discussion

We found histologically proven epithelioid granulomas related to tuberculosis in inguinal lymph nodes, gastrointestinal tract, liver and vertebrae, and ultrasound of the abdomen demonstrated enlarged para-aortic and peripancreatic lymph nodes suggestive of generalized tuberculosis. The 58-year-old patient was probably suffering from postprimary or reactivated gastrointestinal tuberculosis caused by *Mycobacterium bovis*, as demonstrated by polymerase chain reaction and culture. *Mycobacterium bovis* accounts for less than 1% of tuberculosis in hu-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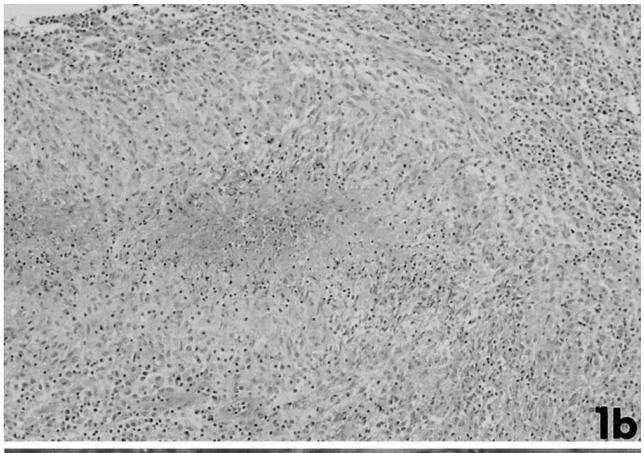
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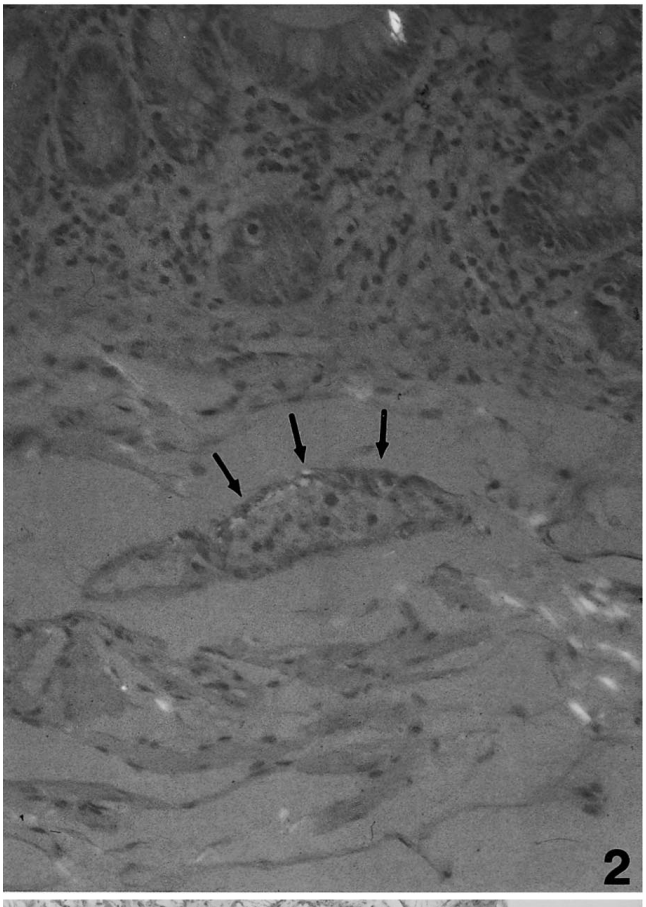
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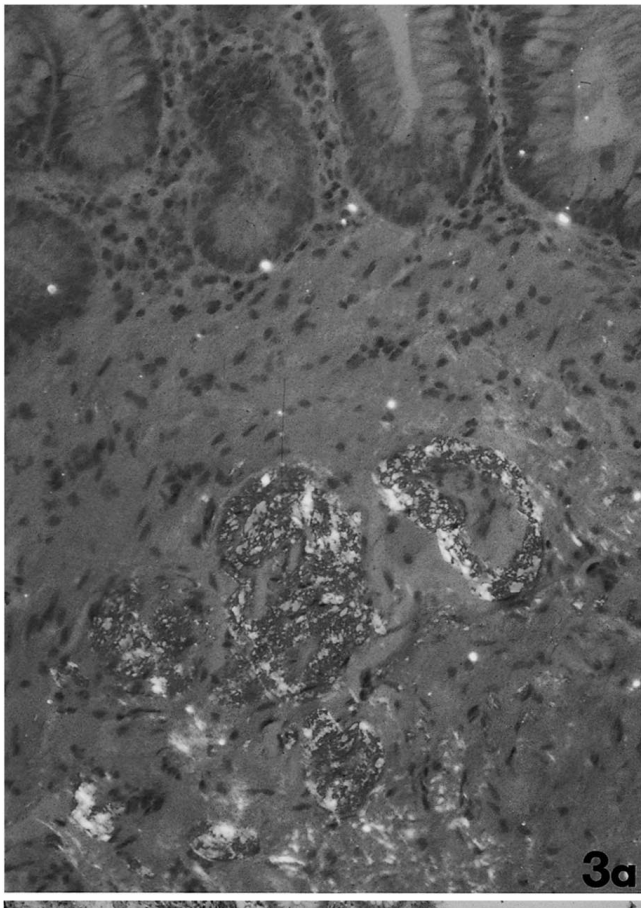
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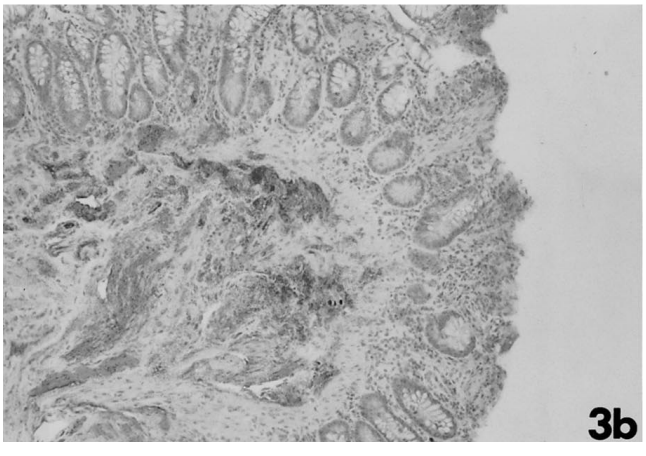
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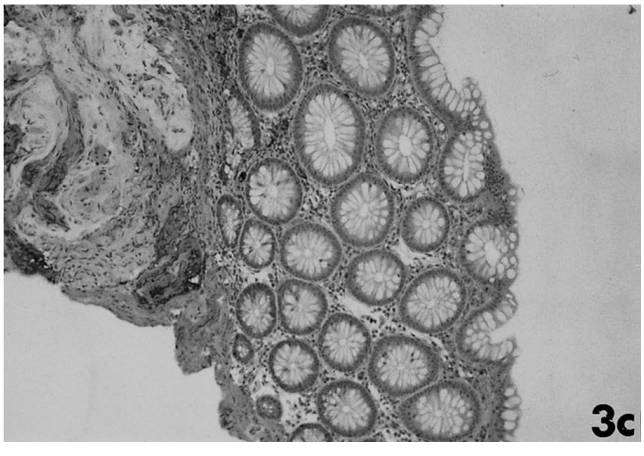
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mans, and a common mode of infection is consumption of contaminated milk. Owing to the ubiquitous use of pasteurized milk and the control of tuberculosis in cattle the incidence of gastrointestinal tuberculosis has declined, and the patient may have suffered from primary gastrointestinal tuberculosis during or immediately after World War II. Reactivation of a quiescent tuberculous complex can occur in elderly patients and, as in the present case, further progression is supported by the anti-inflammatory treatment administered. In general it can be very difficult to differentiate Crohn's disease from gastrointestinal tuberculosis, since the clinical presentations can be very similar and tuberculous granulomas do not always enclose central necrosis [1, 22]. Misinterpretation of gastrointestinal tuberculosis as Crohn's disease over a number of years has been documented previously [33]. However, in the present case tuberculosis was suspected but the gastrointestinal type was not considered at first, and despite the presence of centrally necrotizing granulomas, which do not occur in Crohn's disease, a diagnosis of Crohn's disease was made.

AA-amyloidosis develops only after a sustained or recurrent acute phase response [6, 11, 12, 19, 31], and the activity of the inflammatory disease has a major impact on the response achieved [7, 9]. Whereas the primary tuberculous complex is associated with only an insignificant acute phase response, a modest to significant increase of the serum level of serum amyloid A (SAA) is observed among patients suffering from postprimary tuberculosis, with and without tissue destruction [7]. In our case the time of exposure to a possibly subclinically reactivated tuberculosis prior to the diagnosis of AA-amyloidosis is unknown and the occurrence of the very first deposits remains obscure. AA-amyloid may have already been present before the patient attended her GP's surgery because of the night sweats, abdominal pain and weight loss. Indeed, it is almost impossible to determine the insidious onset of AA-amyloidosis in clinical practice unless patients at risk are identified in advance and screened routinely [9]. Clinical judgement is based primarily on the clinical presentation of the patient and the progress of the underlying disease. From this point of view, scanty deposits of amyloid were evident within 9 months after the first presentation of our patient, which rapidly progressed to generalized AA-amyloidosis and which, in this case, may have been due to generalized tuberculosis with histologically proven necroses in every organ investigated. However, the patient received an anti-inflammatory treatment which suppressed the acute phase response, since CRP was only moderately elevated. This observation may be contradictory to the rapid progress of AA-amyloidosis, but treatment was started after amyloid had already been deposited, so that it would have been impossible for it to exert an influence on amyloidogenesis. It was thought that sufficient anti-inflammatory treatment would have an impact on the progress of the disease, but the opposite was achieved, a discrepancy which is difficult to explain. Hypothetically, these deposits, already present, may have served as a nidus propagating the deposition of amyloid even when the serum level of the precursor protein should have been reduced. However, serum levels of SAA were not investigated in this particular case, and the patient was still suffering from an untreated serious infectious disease. The problem remains unsolved in this case.

Relatively little is known about the time-course and progression of human AA-amyloidosis. Most of our knowledge stems from the murine model of reactive amyloidosis. In mice, AA-amyloidosis can be induced by various different inflammatory stimuli and, depending on the experimental procedure administered, deposits are found after 18 h or a few weeks [14, 24, 35]. Different variables influence the susceptibility, onset and progression of murine amyloidosis, some of them being the primary structure of the precursor protein [35], the type and duration of the inflammatory stimulus [20, 37], the presence of an "amyloid-enhancing factor" (AEF) [24, 25], apolipoprotein E [8, 18, 23], amyloid P component [3], protease inhibitors [39] and some further, still ill-defined, strain-specific genetic variables [4, 13, 38]. Our knowledge of the different variables in mice makes the development of AA-amyloidosis in this model and in the individual mouse strains quite predictable. Analogous knowledge of the human disease could be extremely useful with respect to prevention, early detection and treatment of patients at risk. However, the recognition of patients at risk is a major problem, as is the early detection of amyloid deposits before complications such as renal insufficiency have occurred to limit the medical treatment options (such as the use of methotrexate). The major lesson to be learned from this case is that amyloid can be present even in the first 9 months after the initial clinical presentation of the patient. Even if the presence of AA-amyloid had been considered as early as that in this particular case, there is a strong possibility that a rectal biopsy or subcutaneous fat-aspiration biopsy would have missed the few scanty deposits owing to sampling error. Therefore, it is proposed that in the case of patients whose clinical condition is strongly indicative of amyloidosis, such as patients suffering from long-standing rheumatoid arthritis with persistently elevated inflammatory indicators [9] or postprimary tuberculosis with tissue destruction [7], when there is no histological proof upon presentation a repeat biopsy should be taken during the next 6 months.

Fig. 1 **a** Section through the colon from a right-sided hemicolectomy, showing a severe inflammatory process with **b** centrally necrotizing epithelioid granulomas. Haematoxylin and eosin, **a** ×9.6, **b** ×30

Fig. 2 Sections through the colon from of a right-sided hemicolectomy, showing vascular deposits of AA-amyloid (*arrows*). Congo red staining in polarized light, ×60

Fig. 3 Biopsies from **a**, **b** the ileocolonic anastomosis and **c** the large intestine, showing abundant vascular deposits of AA-amyloid. **a** Congo red in polarized light, ×60 **b**, **c** immunostaining with anti-AA amyloid and haematoxylin counterstain, ×30

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