

Teaching Point
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Whipple's disease: often a late diagnosis and a rare cause of nephropathy

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Introduction

Whipple's disease (WD), first described in 1907 [1], is an uncommon entity caused by *Tropheryma whippeli*, an actinomycete, infecting macrophages. The first isolation of the bacillus was described in 2000 [2]. Massive infiltration of the tissue of affected organs by macrophages staining positive with periodic acid-Schiff (PAS) typifies WD.

Typical findings in WD include fever, nondestructive polyarthritis, abdominal symptoms including diarrhoea and wasting, endocarditis, lymphadenopathy, uveitis and neurological symptoms. By the time of diagnosis, diarrhoea and wasting may be prominent symptoms, but these are usually preceded by a period of migratory arthralgias and myalgias that can last for many years [3]. General physicians rather than gastroenterologists see the patients in this stage of the disease.

Little is known about the epidemiology, but WD is an extremely rare condition, most often affecting middle-aged European males [3]. The microorganism is ubiquitous and has been found in saliva and faeces of both patients and unaffected individuals. The relative lack of inflammatory response at infected sites suggests a defective immune response on exposure to *T. whippeli* in affected patients, but they do not appear to be predisposed to other opportunistic infections [3]. It seems likely that an immunological host factor plays a role in the occurrence of the disease.

Untreated patients may die from wasting or from CNS involvement. Most patients react well to prolonged antibiotic treatment but the prognosis of those who relapse is poor. Initial treatment with ceftriaxone for 2 weeks, followed by oral co-trimoxazole for 1 year, is currently advised [3].

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Case description

A 42-year-old woman was seen with periods of fever, sore throat, myalgias and arthralgias with swellings of the knees that resolved spontaneously. Repeated physical examination revealed no abnormalities. ESR (ranging between 33 and 80 mm/h, normal 0–20) and CRP (ranging between 15 and 105 mg/L, normal 0–10) were elevated, but a full blood count, blood chemistry, urine analysis and thyroid functions, AST, serology for rheumatic arthritis and lupus, *Borrelia* infection, and hepatitis B and C were all normal or negative, as were radiological examinations of chest, abdomen and sinus and a colonoscopy.

Three years later, she presented with fatigue, a weight loss of 6 kg, poor appetite, abdominal discomfort, slight oedema and a period of diarrhoea without mucus or blood. There had been two more episodes of joint complaints but fever had not recurred. Her body weight was 57 kg at a length of 170 cm, blood pressure was 105/70 mmHg and no abnormalities were noticed apart from a slightly distended abdomen and some oedema of the legs. Investigations included ESR 43 mm/h, CRP 65 mg/L, Hb 6.3 mmol/L (7.5–10.0), MCV 82 fL (80–100), ferritin 42 µg/L (10–150), folic acid 6.5 nmol/L (5–25), vitamin B12 149 pmol/L (150–700) and albumin 18 g/L (35–45). The urine tested positive for albumin (1240 mg/L, 169 mg/mmol creatinine).

Upper GI endoscopy showed an abnormal flat appearance and whitish plaques in the descending duodenum and the proximal jejunum. Whitish plaques without erosions or erythema were also seen in the terminal ileum and coecal region at colonoscopy. Biopsy specimens of these plaques showed infiltration with macrophages, staining positive with PAS, establishing the diagnosis of WD (Figure 1). PCR confirmed the presence of *T. whippeli*.

Initial treatment consisted of ceftriaxone 2 g administered intravenously once daily followed by co-trimoxazole 960 mg b.i.d. orally. Because she developed a skin rash and elevation of liver enzymes, an allergy to co-trimoxazole was suspected; therefore, ceftriaxone was restarted. Further, she was started on parenteral nutrition for malnutrition.

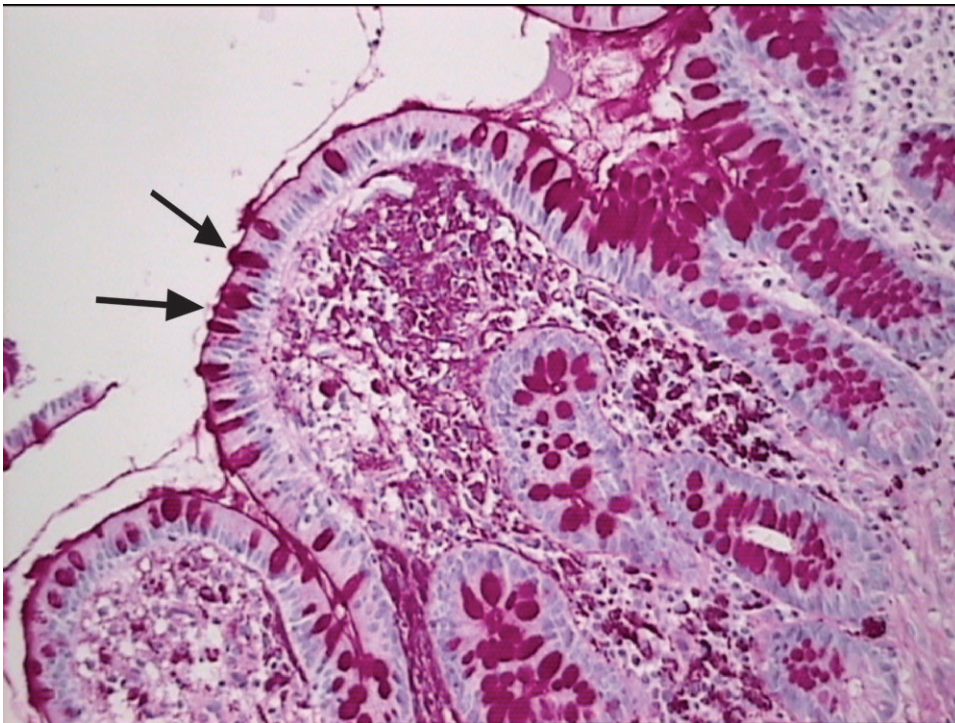


Fig. 1. Jejunal biopsy (200 \times) stained with periodic acid-Schiff. Note the numerous macrophages in the lamina propria (arrows).

During the follow-up, she developed a severe nephrotic syndrome with proteinuria up to 15 g/24 h and serum albumin 8 g/L. The urinary sediment was normal and the creatinine clearance was 120 mL/min. A kidney biopsy showed nine glomeruli with marked eosinophilic mesangial expansion staining positive with Congo red (Figure 2). There was typical apple-green birefringence under polarized light. The interstitium showed no marked infiltrate. The glomerular lesions were positive with a monoclonal antibody directed against amyloid A (Euro Diagnostica, clone: Reu-86.2 Lot no.: BN 2057). The biopsy specimens from the intestines were also stained with Congo red and were positive for amyloid.

A liver biopsy was taken showing hepatic peliosis and numerous PAS-positive macrophages. Findings were interpreted as WD and effects of ceftriaxone and of parenteral nutrition, which were discontinued. Co-trimoxazole was restarted. Hepatic enzymes gradually improved and no skin rash developed.

Six months after the initial diagnosis of WD she is still on treatment with co-trimoxazole. The nephrotic syndrome persists. Creatinine clearance is 60 mL/min. CRP is 13 mg/L; gastrointestinal symptoms are minimal.

Discussion

As with this patient, the diagnosis of WD is frequently made after a prolonged period of unexplained symptoms, at which time late complications may have developed. Renal manifestations of WD have infrequently been reported,

yet have included diverse pathology. Nephropathy may be found early as well as late in the course of the disease.

In a series of 27 patients, proteinuria was found in 11 (37%) and microscopic haematuria in 3 (11%), so urinary abnormalities are not uncommon in WD [4]. It is not known how many patients have urinary symptoms early in the course of WD. Stoll *et al.* [5] described two patients in whom IgA nephropathy was diagnosed several years prior to onset of abdominal symptoms from WD. They propose that WD is a cause of IgA nephropathy and speculate that the infected mucosa of the small bowel produces increased amounts of secretory IgA. Secretory IgA concentrations measured in intestinal aspirates in WD, however, seem normal [3]. A diminished clearance of IgA by hepatic macrophages and by glomerular mesangial cells may favour formation of mesangial deposits. Although studies on macrophage function are sparse there may be a subtle defect in the interplay between macrophages and T cells [3]. IgA nephropathy has been reported in only one more patient with WD (and EBV infection) by Evrenkaya [6]. This paucity of data on renal biopsies probably suggests that glomerulonephritis is under-reported in WD.

'Sarcoidlike granulomas' have been described both early in the course of WD, i.e. before onset of abdominal symptoms, and in progressive disease. Multiple noncaseating granulomas have been found in the liver [7], the lungs [7,8] and in the kidneys [9,10] of patients before a diagnosis of WD was established. Depending on the biopsied organ and the clinical setting, the finding of granulomas makes a broad differential diagnosis. Hilar lymphadenopathy, increased ACE, increased uptake of gallium 67 by the lungs and even temporary response to corticosteroids can make

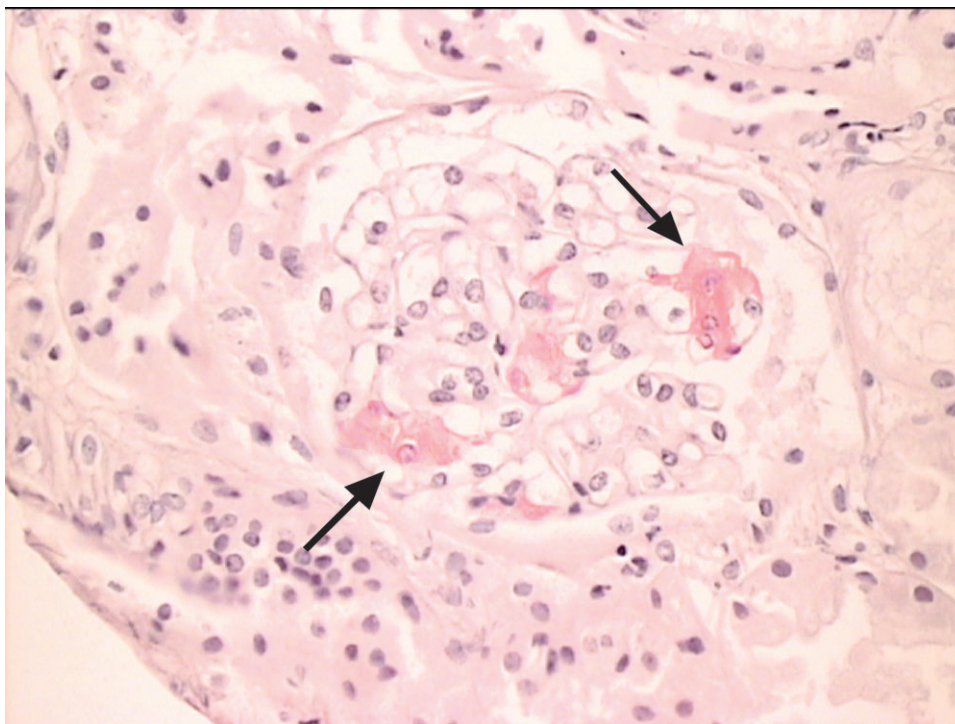


Fig. 2. Congo red stain of renal tissue (400×), showing positive staining of mesangial depositions (arrows). Under polarized light (not shown) these lesions had typical apple-green birefringence diagnostic for amyloidosis.

WD mimic sarcoidosis [7,8]. Granulomas may easily be diagnosed as sarcoidosis in the absence of another likely primary cause. In patients with idiopathic granulomas WD is, therefore, a serious consideration, even in the absence of 'typical' symptoms.

Secondary amyloidosis is a late complication of chronic inflammatory disorders like rheumatoid arthritis, spondylitis, chronic infections and Crohn's disease [11]. Most patients present with renal symptoms. Secondary amyloidosis in WD has occasionally been described during life [12] and at autopsy [13]. Depositions of amyloid were seen in several organs, including the kidneys. The nephrotic syndrome has been described in only two WD patients [14,15]. Amyloid was found in both renal (glomerular and vascular) and intestinal localizations. Unexplained rheumatic complaints in these patients had existed for 15 and 30 years, respectively. Early diagnosis and adequate antibiotic treatment, therefore, seem essential to prevent the development of amyloidosis in WD.

The prognosis of secondary amyloidosis is poor with a median survival after diagnosis of 133 months [11]. However, successful treatment of the underlying inflammatory disease may be beneficial. Renal failure developed in the patient described by Leidig [15], although WD responded to antibiotic treatment. In the patient described by Cruz [14], kidney function was maintained and proteinuria gradually diminished after 1 year. Interestingly, 5 years after the initial diagnosis, the patient was asymptomatic and a rectal biopsy for amyloidosis was negative.

The patient we describe appears to be the third reported with nephrotic syndrome due to secondary amyloidosis

in WD. Compared to the two other reported patients, the period with undiagnosed complaints was relatively short (3–4 years). After the start of appropriate treatment, gastrointestinal problems have much diminished and CRP has almost normalized. Yet the nephrotic syndrome is still severe and the prognosis of renal function is uncertain.

Teaching points

1. Whipple's disease is often a late diagnosis; early diagnosis and adequate antibiotic treatment seem essential to prevent development of secondary amyloidosis.
2. Adequate treatment of Whipple's disease may lead to remission of proteinuria and resolution of the depositions of secondary amyloid.
3. Nephropathy in the early stages of Whipple's disease (before onset of abdominal symptoms) may include IgA nephropathy and granulomatous interstitial nephritis mimicking sarcoidosis.

Conflict of interest statement. None declared.

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