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Mini Review

Whipple's Disease: An Elusive Diagnosis of a Multisystem Presentation

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Abstract

A 45-year-old female presented with diarrhoea and low-grade fever then progressively developed a constellation of seemingly unrelated symptoms and signs involving multiple body systems. Whipple's disease was eventually diagnosed after lymph node and small bowel biopsies demonstrated periodic acid-Schiff stain positive macrophages. This case exemplifies the broad range of manifestations of this disease which contributes to its difficult, and often delayed, diagnosis.

Keywords: Whipple's disease; diarrhea; lymph node; elusive diagnosis; multisystem presentation; CSF

Introduction

A 45-year-old female began to experience abdominal cramps, loose bowel motions and a low-grade fever when returning to Australia from a three-week trip to Spain. She consulted her general practitioner (GP) who prescribed ciprofloxacin for traveler's diarrhoea. After the patient failed to improve, her GP arranged for basic bloods, stool microscopy and culture plus gastroenterology referral. The tests demonstrated a haemoglobin of 90g/L and C-reactive protein of 200mg/L with normal electrolytes, renal and liver function. Stool was negative for blood, bacteria, and parasites. Physical examination revealed tanned complexion of the neck and arms and a soft non-tender abdomen.

At consultation with the gastroenterologist the patient had lost 6 kilograms over 6 weeks. Clinical history did not reveal any obvious risk factors for infectious diarrhoea during the recent travel. The diarrhoea was described as persisting day and night with associated abdominal cramps which were not lessened by defecation and there was no loss of appetite. Further investigation of stool was organised comprising osmolar gap, stool fats, faecal elastase, calprotectin, microsporidium, amoebiasis, giardiasis, and cryptosporidium. An HIV test and coeliac screen were also performed. Endoscopies were arranged with normal macroscopic appearance and biopsy results.

The patient subsequently started to experience pain in the shoulders and knees. In view of her joint pain and skin pigmentation she was also referred to a rheumatologist and endocrinologist. Joint examination did not demonstrate any effusions or limitation in mobility. The rheumatologist arranged for autoimmune studies including antinuclear antibody, citrulline antibody, Rheumatoid factor, antineutrophil cytoplasmic antibodies, double-stranded DNA antibody, anti-Ro antibody as well as joint magnetic resonance imaging (MRI). Further investigations were requested by the endocrinologist including chromogranin A, eosinophils, thyroid function tests, calcitonin, serum gastrin, vasoactive intestinal peptide, cortisol plus a Synacthen test.

The results of the aforementioned studies were either negative or within normal limits. A computed tomography scan of the abdomen was performed, and the result was unremarkable. The patient continued to experience arthralgias, low-grade fevers and diarrhoea. She progressed to 10 kilograms of weight loss over 10 weeks and so was admitted to hospital for further investigation and multidisciplinary review. Around this time, the patient reported experiencing central chest pain, so an electrocardiogram was performed which demonstrated widespread ST-elevation and PR-segment depression. Troponin, creatine kinase and B-type natriuretic peptide were normal, as was an echocardiogram, and a diagnosis of pericarditis was made. The patient was commenced on colchicine and prednisolone.

In addition, the patient then developed a rigid gait and impaired vertical eye movement, consistent with supranuclear gaze palsy. Detailed neurological examination was otherwise unremarkable. She was referred to a neurologist specialising in movement disorders. An MRI brain and lumbar puncture were performed. Imaging was normal and the cerebrospinal fluid (CSF) result was acellular with normal protein and negative for bacteria and viruses. The patient was trialed on levodopa without improvement, so the medication was ceased.

Consequently, the patient then began to experience a rapid decline in short-term and remote memory. MRI brain was repeated without any new

finding of abnormality and repeat CSF did not support a diagnosis of autoimmune encephalitis or Creutzfeldt-Jakob disease. In the meantime, she continued to have persistent diarrhoea and weight loss. Repeat faecal testing revealed increased fats and deficient faecal elastase.

The patient went on to develop a generalized lymphadenopathy. A surgical biopsy of an axillary lymph node was performed and sent for histology, flow cytometry, immunohistochemistry and microbiological examination including staining for acid-fast bacilli. Importantly, macrophage staining was positive with periodic acid-Schiff (PAS). Subsequent biopsies of the duodenum from upper endoscopy demonstrated excessive macrophages stained positive for PAS. This confirmed a diagnosis of Whipple's disease.

The patient was commenced on ceftriaxone for four weeks followed by trimethoprim and sulfamethoxazole for two years with a good outcome.

Discussion

Whipple's disease is a rare disease caused by infection with Tropheryma whipplei, a gram-positive, intracellular, non-acid-fast bacillus which is a recognised cause of culture negative endocarditis.[1] The bacterium has been identified in the stool and saliva of asymptomatic carriers and only a small percentage develop symptomatic disease.[2,3] Whipple's disease has been most commonly reported in middle aged white males however the prevalence may actually be similar between the sexes, in addition to increasing with age [4].

Whipple's disease has a wide spectrum of symptomatology due to its multisystem involvement. Commonly there is a long prodromal phase with non-specific symptoms, usually joint discomfort. [5] Classic Whipple's disease is typified by arthralgias or arthritis, diarrhoea with malabsorption and weight loss [6].Fever and abdominal pain may be present, and other common features include neurological symptoms, elevated inflammatory markers, and anaemia [7].

The documented range of clinical manifestations is broader still, including lymphadenopathy, melanoderma, uveitis, pleural effusion, as well as cardiac involvement including endocarditis and pericarditis [6].The result is a disease that may mimic a broad spectrum of other infectious and non-infectious conditions.

The neurological manifestations in particular are wide-ranging and include cognitive change, supranuclear ophthalmoplegia, ataxia, neuropsychiatric and hypothalamic symptoms, myoclonus and seizures [8].Movement disorders are common, and oculomasticatory myorhythmia and oculofacial-skeletal myorhythmia are pathognomonic of Whipple's disease [9].Neurological deficits may persist despite appropriate treatment [10].

Cutaneous features of Whipple's disease include hyperpigmentation, or melanoderma, due to niacin or hypocortisolism, purpura due to vitamin C or K deficiency, oedema due to hypoproteinaemia and inflammatory skin eruptions [11, 12].

In classic Whipple's disease there is massive infiltration of the lamina propria of the intestine with T. whipplei-infected macrophages, the ability of the macrophages to kill the bacteria is impaired leading to its replication and spread [13].macroscopic appearance at endoscopy is commonly normal but pathological findings include dilated villi and lymphectasia P [14].

PAS staining of small intestinal biopsy has been the standard diagnostic test for classic Whipple's disease since PAS-positive inclusions in macrophages, and the subsequent correlation with the occurrence of T. whipplei bacilli in the cytoplasm, was first described in 1949.[15] Ziehl-Neelsen staining, for which T. whipplei are negative, can help discriminate from Mycobacterium species.[6] Polymerase chain reaction (PCR) and specific immunohistochemistry may be utilised as confirmatory diagnostic tests [14].

However, PAS staining of small bowel tissue is more likely to be negative in cases with minimal gastrointestinal symptoms, so PCR assay should be performed on affected extraintestinal tissue specimens such as synovial and cerebrospinal fluid [15]. Culture of the bacterium, first achieved in 2000, remains impractical due to the very slow replication rate [1].

Due to its heterogenous presentation and rarity, the diagnosis of Whipple's disease after the onset of symptoms is commonly delayed, for example in a series of 142 patients the average time to confirmed diagnosis was 6.4 years [7].Patients may be misdiagnosed to deleterious effect, for example as having inflammatory rheumatologic disease, for which commencing immunosuppressive therapy can hasten clinical deterioration in Whipple's disease [5].

It is prudent to include Whipple's disease in the differential for patients presenting with a broad range of symptomatology particularly if more common pathologies have been excluded [5].Earlier diagnosis of Whipple's disease may lead to improved mortality and reduced relapse rates, without treatment the disease is inevitably fatal [16].

The treatment of Whipple's disease consists of antibiotic therapy such as ceftriaxone, trimethoprim with sulfamethoxazole and doxycycline, with penetration of the blood-brain barrier desired [3].There is usually rapid clinical improvement however prolonged antibiotic courses are required for eradication [17]. Disease relapse can occur years after the completion of antibiotic therapy so ongoing follow up is recommended [17].

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