Rare disease

Whipple's disease presenting with neurological symptoms in an immunosuppressed patient

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Summary

We report an unusual case of Whipple's disease, which remained undiagnosed for several years in a patient being treated with immunosuppressive therapy for many years. The patient presented with a purpuric rash, neurological symptoms, lymphadenopathy and gastrointestinal symptoms. The diagnosis was made by endoscopic biopsy of the duodenum with periodic acid Schiff staining, as well as PCR testing on blood and cerebrospinal fluid. The patient was successfully treated with intravenous ceftriaxone, followed by oral cotrimoxazole for 1 year.

BACKGROUND

Whipple's disease is a rare, multisystemic chronic infectious disease. The disease preferentially affects middle-aged white men, with an annual incidence of less than 1 per million.^{1 2} The causative organism is a Gram-positive bacillus named *Tropheryma whippelii*. Clinical manifestations of Whipple infection seem to occur in the presence of low activity of T1-helper cells.³ The typical clinical manifestations of Whipple's disease are malabsorption syndrome, with chronic diarrhoea, weight loss and abdominal pain, often preceded by long-standing signs of arthralgia/arthritis of the large joints. Other symptoms include hyperpigmentation of the skin, subcutaneous nodules, lymphadenopathy, fever and the involvement of the heart, the central nervous system or the eyes.^{1 4 5} We describe a patient with a variety of symptoms of Whipple's disease probably worsened by his immunosuppressive therapy.

CASE PRESENTATION

A 52-year-old-man with a long-standing history of psoriatic arthritis treated with different immunosuppressive drugs presented to our hospital with a vasculitis-like skin disease. The diagnosis of psoriatic arthritis was based on a symmetric poly-arthritis and psoriasis for 25 years. He had been forced to end his profession as a painter due to rheumatic complaints 7 years before transfer to our hospital. At first his arthritis responded well to the given immunosuppressive therapy, but in 2006 even drugs such as etanercept and adalimumab failed.

His medical history further revealed that he had developed symptoms of aphasia and paraesthesia of his right hand 2 years before, following a third course of intravenous treatment with infliximab for his arthritic symptoms. At that time a CT scan of the head was performed, which revealed a left posterior cerebral artery infarction of older age; treatment with acetylsalicylic acid was started. Electromyography was consistent with an ulnar neuropathy at the elbow. During the last years his speech had

gradually deteriorated and the patient suffered from frequent headaches and dizziness. A skin biopsy had been performed several weeks earlier and showed a non-specific chronic perivascular inflammation. The skin disease seemed to resolve by a prednisone treatment by his rheumatologist. Although his skin condition improved, the patient suffered from diarrhoea, up to eight times daily without blood or mucus and with abdominal pain and a 7 kg weight loss over the past 2 weeks. Furthermore, he experienced progressive weakness of his right arm, dysarthria and facial palsy, for which he was admitted. On admission, our patient took methotrexate 15 mg per week, prednisone 30 mg, acetylsalicylic acid and folic acid.

On physical examination, the patient did not appear acutely ill. His blood pressure was 125/78 mm Hg, with a regular pulse rate of 88 beats per minute. His temperature was 37°C. Skin examination showed multiple purpura and petechiae mostly on the extremities. The abdominal examination was without abnormalities. Neurological examination revealed cognitive slowness and dysarthria. Examination of the cranial nerves revealed a subtle right-sided facial palsy. There was a visual extinction on the right and a hypertonic paresis of the right arm (MRC grade 4). In addition, he had diminished sensation for pain AND light touch on the fourth and fifth fingers on the right hand consistent with an ulnaropathy. Deep tendon reflexes were brisker on the right limbs. Jerks of the knee and ankle were symmetrical and plantar responses were flexor.

INVESTIGATIONS

An extensive laboratory investigation was performed: the erythrocyte sedimentation rate was 18 mm/h, haemoglobin 6.2 mmol/l, mean cell volume 92 fl, reticulocytes $186 \times 10^9/l$, haptoglobin 3.36 g/l, sodium 132 mmol/l, kalium 3.4 mmol/l, urea 6.6 mmol/l, creatinine 79 µmol/l, normal liver enzymes, C reactive protein 27 mg/l, albumin 24.4 g/l, normal autoimmune serology, ACE 27 U/l, HLA B27 neg. and normal urine test.

MRI scan of the head showed abnormalities that relatively spare the cortical areas consistent with multiple infarctions of older as well as recent age (figure 1). A diagnosis of vasculitis was suggested. CT scan of the chest and abdomen showed, in addition to mediastinal and para-aortal lymphadenopathy, multiple pulmonary emboli, which were not suspected before on clinical grounds. A lumbar puncture was performed. Cerebral spinal fluid showed a leucocyte count of 3/3 per mm³, glucose 3.2 mmol/l and protein level 200 mg/l. PCR detected no JC virus DNA in the spinal fluid. Because of the progressive neurological symptoms and lymphadenopathy, a diagnosis of lymphoma or vasculitis was considered and treatment was started with high doses of methylprednisolone. The symptoms of our patient seemed to resolve. Lymph node resection was performed by mediastinoscopy; microscopic examination showed lymph node tissue with mucus-containing macrophages, which were initially considered as non-specific and reactive by the pathologist. A CT guided biopsy of a para-aortal lymph node yielded inconclusive material for diagnosis. Our patient left hospital against medical advice because of psychological problems. However, after 1 week he was re-admitted with progressive diarrhoea, abdominal pain and hypotension. Upper endoscopy showed duodenitis with extensive lymphangiectasia. Biopsy of the duodenum demonstrated fields of macrophages with abundant cytoplasm. In the periodic acid Schiff (PAS)-stained slides, macrophages contained small micro-organisms, as seen in Whipple's disease. Revision of the earlier lymph node

biopsy now disclosed similar foamy macrophages compatible with Whipple's disease. PCR of *T. whippelii* on biopsies and cerebral spinal fluid were all positive, confirming the diagnosis of Whipple's disease.

TREATMENT

Treatment with intravenous ceftriaxone 2000 mg once daily for 2 weeks was initiated, followed by oral co-trimoxazole 960 mg twice daily. Although his gastrointestinal symptoms as well as his skin disease resolved rapidly, his neurological condition did not improve. The patient was discharged from hospital and co-trimoxazole was continued for a year and prednisolone was gradually tapered to a dose of 7.5 mg per day.

OUTCOME AND FOLLOW-UP

Neuropsychological examination after discharge revealed serious cognitive sequelae with impairment in memory, attention and executive functioning. Six months after discharge, the patient complained of frequent headaches. An additional MRI scan of the brain was performed, showing findings similar to the earlier imaging. A follow-up lumbar puncture revealed no abnormalities, and PCR for *T. whippelii* of the cerebral spinal fluid was negative.

DISCUSSION

Whipple's disease is a rare condition with a broad spectrum of symptoms that can mimic many other chronic inflammatory diseases. The non-specific clinical features and low incidence of the disease often lead to delayed diagnosis. Untreated, Whipple's disease can be fatal. Although appropriate antibiotic therapy generally leads to rapid improvement and to lasting remission, neurological symptoms are often irreversible.¹⁻⁵ Diagnosis is made by a combination of tests. Upper gastrointestinal endoscopy of the small intestine is the diagnostic test of choice.¹ In our patient, endoscopic examination of the duodenal mucosa showed a characteristic pale yellow surface with clumsy and dilated villi with ectatic lymph vessels. Whipple's disease can also present without the described macroscopic abnormalities, in which case extended analysis of multiple biopsies using PAS staining can lead to the diagnosis.¹⁻⁵ Biopsy material is characterised by the presence of foamy macrophages in the lamina propria. The macrophage cytoplasm contains large amounts of particles that are PAS positive.¹⁻⁴ The PAS-positive inclusions, however, are non-specific; for example, such inclusions can also be found in *Mycobacterium avium* complex infection. Moreover, as the duodenal lesions can be focal, multiple biopsies should be studied when the diagnosis is suspected on clinical grounds. Depending on clinical manifestations other tissues might be biopsied.² In our patient we found foamy macrophages with positive PAS staining in the lymph nodes and PAS-positive macrophages in the intestinal mucosa.

The causative agent of Whipple's disease, *Tropheryma whippelii*, can also be detected by PCR. PCR testing has a high sensitivity, up to 96.6% with S rRNA testing PCR.⁶ However, *T. whippelii* PCR has occasionally been found to be positive in patients without the classic clinical or histological features of Whipple's disease. The exact prevalence of healthy carriers of *T. whippelii* is unknown, with estimates ranging as widely as 0.6–35%. Probably there are

Figure 1 MRI scan of the head, showing multiple infarctions of older as well as recent ages.

many false-positive results in healthy carriers due to a lack of specificity of different designed primers in PCR testing.^{1 7 8}

In our patient there was a delay in diagnosis due to a non-classical presentation with a skin disease, neurological symptoms and lymphadenopathy. At first his gastrointestinal symptoms were not prominent and his arthritis was attributed to his psoriatic arthritis. Whipple's disease has traditionally been regarded as a gastrointestinal disease, but in most cases the disease starts insidiously with arthropathy.³ In our patient, clinical findings were consistent with psoriatic arthritis for many years. However, from 2006 onwards there was some discrepancy between objective and subjective symptoms and therapy failed. It remains unclear whether the rheumatological findings were attributable to Whipple's disease from the start. In one study arthropathy was the first symptom in 63% of patients preceding the final diagnosis by a mean of 8 years.^{3 9} In our patient, purpuric skin disease, a well-known manifestation of Whipple's disease, was prominent.^{1 10}

Neurological manifestations occur in 10–43% of the patients with multisystem Whipple's disease.¹¹ The cerebral cortex, hypothalamus and midbrain are most commonly invaded, although the cerebellum, spinal cord and peripheral nervous system can be affected too. Signs of central nervous system infection include cognitive changes, supranuclear gaze palsy, altered levels of consciousness and movement disorders. In the case of signs of central nervous system infection, an MRI scan of the head should be performed as the capability of detecting smaller or contrast-enhancing lesions using CT scanning is inferior to that using MRI.^{12 13} Whipple's disease mainly affects middle-aged white men. A genetic susceptibility is suggested by the three to four times increased prevalence of HLA B27 positivity.³ In patients with Whipple's disease, subtle persistent defects of cellular immunity have been observed, involving activation and interaction of macrophages and T cells. This defect can result in disturbed phagocytosis and intracellular degradation of *T. whipplei*, allowing the spread of the bacillus from the gastrointestinal mucosa to peripheral organs. The precise mechanisms involved are still unknown. It might even be that some of these immunological defects could be secondary instead of primary to the Whipple infection.⁹ In our patient classical symptoms of Whipple's disease developed after treatment with methotrexate, prednisone and infliximab, which is in accordance with the recent literature.⁹

Thus, treatment with immunosuppressive drugs might have been the trigger for disease activity in this case. A few similar case reports suggest that Whipple's disease may occur in a setting of immunodeficiency or immunosuppression.³ In one study immunosuppressive treatment of arthropathy was associated with the onset of diarrhoea in Whipple's disease.⁹ In our patient, tumour necrosis factor- α inhibition seemed to have facilitated a rapid deterioration of his clinical condition, reminiscent of the rapid reactivation of latent tuberculosis in rheumatoid arthritis patients.^{14 15} In the present case, rapid dissemination of *T. whipplei* might have been provoked by inhibiting some immune defence mechanisms important in coping with intracellular infections. Thus, TNF- α

influences the maturation of inflammatory cells and induces apoptosis of infected cells and granuloma formation,¹⁴ both of which mechanisms play important roles in Whipple's disease.¹⁶

The optimal antibiotic regimen and duration of therapy in Whipple's disease are still subject to discussion. No randomised clinical trials have been performed in patients with Whipple's disease. Historical data have shown frequent relapses with tetracyclines, especially in patients with neurological symptoms. In two studies co-trimoxazole has shown to be superior, especially in patients with neurological symptoms. To completely eradicate Whipple's disease from the central nervous system, an induction therapy with ceftriaxone or penicillin G parenteral for 14 days has been suggested.^{1 17 18} Our patient has been treated in accordance with these guidelines.

In retrospect, the diagnosis in our patient was delayed due to the prominence of non-classical symptoms. The initiation of high dosages of immunosuppressive agents appears to have been the trigger for disease activation. Clinicians should include Whipple's disease in their differential diagnosis of a broad spectrum of symptoms, especially in patients treated with immunosuppressives or patients showing deterioration after the initiation of immunosuppressive therapy.

Learning points

- Whipple's disease is a rare condition with a broad spectrum of symptoms which often leads to delayed diagnosis.
- Neurological manifestations occur in 10–43% of patients with multisystem Whipple's disease.
- Although appropriate antibiotic therapy generally leads to rapid improvement and to lasting remission, neurological symptoms are often irreversible.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Schneider T**, Moos V, Lodenkemper C, et al. Whipple's disease: new aspects of pathogenesis and treatment. *Lancet Infect Dis* 2008;**8**: 179–90.
2. **Fenollar F**, Puechal X, Raoult D. Whipple's disease. *N Engl J Med* 2007;**356**:55–66.
3. **Marth T**, Raoult D. Whipple's disease. *Lancet* 2003;**361**:239–46.
4. **Zaaijer HL**, Savelkoul PH, Vandenbroucke-Grauls CM. Whipple's disease. *Ned Tijdschr Geneesk* 1999;**143**:388–92.
5. **Smit EG**, Ferwerda J, Dekker W. Whipple's disease in a man with weight loss and diarrhea. *Ned Tijdschr Geneesk* 1999;**143**:413–17.
6. **Ramzan NN**, Loftus E, Burgart LJ, et al. Diagnosis and monitoring of Whipple disease by polymerase chain reaction. *Ann Intern Med* 1997;**126**:520–7.
7. **Dutly F**, Altwegg M. Whipple's disease and "Tropheryma whipplei". *Clin Microbiol* 2001;**14**:561–83.
8. **Rolain JM**, Fenollar F, Raoult D. False positive PCR detection of Tropheryma whipplei in the saliva of healthy people. *BMC Microbiol* 2007;**7**:48.
9. **Mahnel R**, Kalt A, Ring S, et al. Immunosuppressive therapy in Whipple's disease patients is associated with the appearance of gastrointestinal manifestations. *Am J Gastroenterol* 2005;**100**:1167–73.
10. **Peters G**, du Plessis DG, Humphrey PR. Cerebral Whipple's disease with a stroke-like presentation and cerebrovascular pathology. *J Neurol Neurosurg Psychiatry* 2002;**73**:336–9.

11. **Panegyres PK**, Edis R, Beaman M, *et al*. Primary Whipple's disease of the brain: characterization of the clinical syndrome and molecular diagnosis. *QJM* 2006;**99**:609–23.
12. **Louis ED**, Lynch T, Kaufmann P, *et al*. Diagnostic guidelines in central nervous system Whipple's disease. *Ann Neurol* 1996;**40**:561–8.
13. **Louis ED**. Whipple disease. *Curr Neurol Neurosci Rep* 2003;**3**:470–5.
14. **Kneitz C**, Suerbaum S, Beer M, *et al*. Exacerbation of Whipple's disease associated with infliximab treatment. *Scand J Rheumatol* 2005;**34**: 148–51.
15. **Harris J**, Hope JC, Keane J. Tumor necrosis factor blockers influence macrophage responses to *Mycobacterium tuberculosis*. *J Infect Dis* 2008;**198**:1842–50.
16. **Desnues B**, Ihrig M, Raoult D, *et al*. Whipple's disease: a macrophage disease. *Clin Vaccine Immunol* 2006;**13**:170–8.
17. **Buckle MJ**, Ellis RW, Bone M, *et al*. Neurologically presenting Whipple disease: case report and review of the literature. *J Clin Pathol* 2008;**61**:1140–1.
18. **Moos V**, Schneider T. Changing paradigms in Whipple's disease and infection with *Tropheryma whipplei*. *Eur J Clin Microbiol Infect Dis* 2011;**30**:1151–8.

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