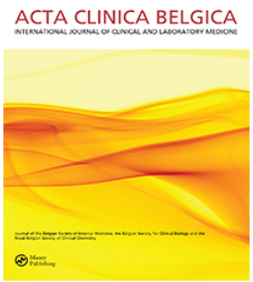

Acta Clinica Belgica
International Journal of Clinical and Laboratory Medicine

ISSN: 1784-3286 (Print) 2295-3337 (Online) Journal homepage: http://www.tandfonline.com/loi/yacb20

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To cite this article: I. Nubourgh, F. Vandergheynst, P. Lefebvre, A. Lemy, N. Dumarey & G. Decaux (2008) AN ATYPICAL CASE OF WHIPPLE'S DISEASE: CASE REPORT AND REVIEW OF THE LITERATURE, Acta Clinica Belgica, 63:2, 107-111, DOI: 10.1179/acb.2008.63.2.009

To link to this article: http://dx.doi.org/10.1179/acb.2008.63.2.009

Case Report

AN ATYPICAL CASE OF WHIPPLE'S DISEASE: CASE REPORT AND REVIEW OF THE LITERATURE

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Key words: Whipple's disease, uveitis, C reactive protein, aqueous humour, fever of unknown origin

ABSTRACT

We report the case of a 57-year-old man, presenting with bilateral panuveitis, bilateral sacroiliitis, intermittent pyrexia and a pulmonary nodule. The patient had been under immunosuppressive treatment for 2 years for Behçet's disease. However, he did not fulfill the diagnostic criteria of Behçet's disease. Blood analysis showed a very high C reactive protein (CRP at 34 mg/dl).

In view of severe intra-ocular inflammation, the anterior chamber was punctured. Polymerase chain reaction (PCR) on the aqueous humour and on the blood revealed the presence of *Tropheryma whippelii* DNA, an agent responsible for Whipple's disease. The patient was treated with ceftriaxone followed by trimethoprim-sulfamethoxazol for 1 year with good clinical and biological evolution.

This case illustrates the difficulty to diagnose an atypical Whipple's disease.

In cases of uveitis with atypical signs and/or not responding to the treatment, the internist must consider to perform an analysis of the ocular fluids.

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INTRODUCTION

Whipple's disease is a rare infectious disease. The classic symptoms are diarrhoea, weight loss and arthralgias but the disease can affect any organ with very variable and atypical symptoms. We report here the case of a man who presented with an exceptional form of the disease consisting in bilateral panuveitis, sacroiliitis, pyrexia and a pulmonary nodule. The patient was exposed to immunosuppressive therapy for a misdiagnosis of Behçet's disease with partial clinical amelioration and regression of inflammatory parameters. The histology of duodenal biopsies was normal. The diagnosis was made by the positivity of the PCR for *Tropheryma whippelii* in the blood and in the aqueous humour.

CASE REPORT

A 57-year-old man was admitted to the department of general internal medicine with bilateral uveitis, recurrent pyrexia and spondylarthralgias.

The patient's medical history revealed grand mal epilepsia treated since chilhood.

Two years before admission, the patient presented with an episode of urethritis, followed by the appearance of uveitis first, treated with corticoid drops. Later, spondylarthralgias appeared. On the basis of severe bilateral uveitis, spondylarthralgias, deep venous thrombosis and 1 episode of genital aphthae. A diagnosis of Behcet's disease was made by an ophthalmologist in Brazil, where the patient used to live. The results of the blood samples from Brazil revealed the presence of major inflammatory parameters, and CRP of approximately 20 mg/dl, regressing under treatment with methotrexate.

The patient's treatment at admission consisted in 40 mg prednisolone/d, 700 mg cyclosporine/d, 1 g sodium valproate/d, 100 mg phenobarbital/d, 12,5 mg warfarin/d, prednisolone forte drops and 70 mg alendronate/week.The patient was Belgian and had been living in Brazil for the last 15 years. He did not smoke.

On admission, the patient complained of reduced visual acuity, pain in the eyes, spondylarthralgias and fever. He described intermittent fever, over a period of a few months, with thermic lysis when the corticotherapy was intensified. He did not present with any major gastrointestinal problems except for an episode of self-limiting diarrhoea 10 days before admission. The patient never had oral aphtae.

On physical examination, the facies was cushingoid and the lower members amyotrophic. The blood pressure was 140/80 mmHg. Temperatures up to 38,8°C were observed during hospitalisation. The conjonctives were erythematous. The oral mucous membrane was normal. Cardiopulmonary auscultation was normal. Abdominal examination revealed left lower quadrant sensibility. The neurological examination was normal. The blood analysis revealed a CRP at level of 34 mg/dl and a count of 20 400 white blood cells/mm3 with 90% of neutrophils. Renal function and liver enzymes were normal. Others parameters were not helpful. Chest X-ray was normal. Urine culture was negative. Despite the presence of a major inflammatory state which is unusual in systemic non-infectious inflammatory diseases but more usual in infectious diseases1, the first diagnostic hypothesis was an inflammatory disease. The duration of the symptoms also plaided for a non-infectious inflammatory disease(2). The patient did not fullfill Behçet's criteria (3) but his condition had responded previously to methotrexate. Thus, at first, we increased the immunosuppressive therapy, without empiric antibiotherapy. Prednisolone doses were increased to 60 mg/day. Ciclosporin(4,5) was maintained at a daily dose of 450 mg. Sulfasalazine(6,7) was introduced at a daily dose of 1 g. Methotrexate was reintroduced at a weekly dose of 15 mg. In the same time, supplementary examinations were performed to exclude an infectious disease and to establish a diagnosis (table 1). The abdominal CT scan showed several jejunal mesenteric enlarged lymph nodes.The chest CT scan showed an aspecific pulmonary nodule of 1,7 cm in the right lung. The 18F- Fluorodesoxyglucose (FDG)-PET/CT showed a hypermetabolic activity of the pulmonary nodule, of a nodular formation in the left upper quadrant and along the duodenum. The 18F-FDG-labeled leukocyte PET/CT (in investigation in our institution9) did not show any deep seated lesions with increased uptake.

Table 1 : Complementary examens

Haemoculture: negative
Tuberculinic intradermoreaction: negative
Coproculture: negative
Syphilitic, HCV and HIV serologies: negative
HLA typing: A2 A29 B45 B40
ANF, ANCA, FR: negative
Chest X-ray: normal
Cardiac ultrasound: normal
Abdominal CT scan: several jejunal mesenteric enlarged lymph nodes.
Chest CT scan: aspecific pulmonary nodule of 1,7 cm in right lung
18F-FDG-labeled leukocyte PET/CT: no deep seated lesions with increased uptake.
18F-FDG PET-CT: hypermetabolic activity of the pulmonary nodule, of a nodular formation in the left hypochondrium and along the duodenum.
Sacroiliac joints CT scan: bilateral asymetrical sacroiliitis

Ophthalmological examination revealed a visual acuity of 1/10 in the right eye and 7/10 in the left eye. Ocular pressure was normal. The slit-lamp examination showed signs of intraocular inflammation in both eyes. The anterior segment showed inflammatory cells in suspension in the aqueous humour, bilateral white granulomatous retrocorneal precipitates and bilateral active iridocrystalline synechiae. Investigation of the posterior segment showed vitritis. The fluorescein an-

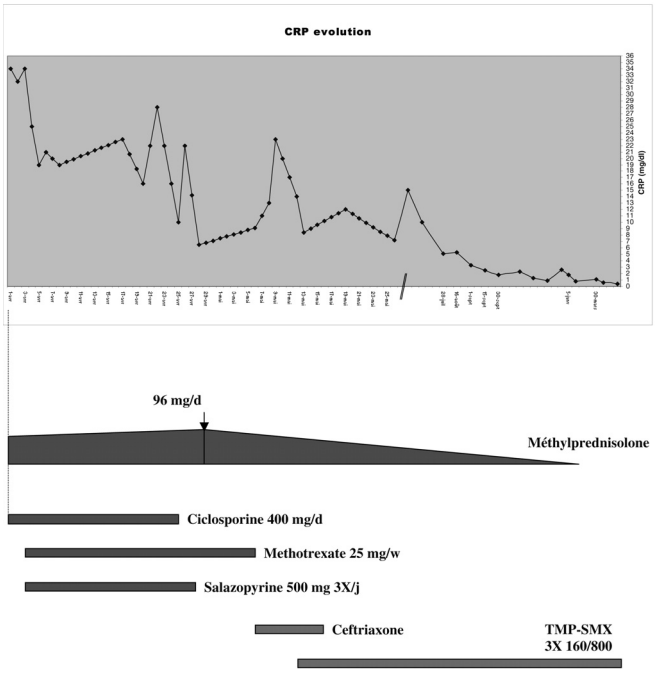

Figure 1. *Evolution of CRP in relation with modification of treatment*

giography showed bilateral papilloedema, right macular oedema and circular spotty bleeding at the right posterior pole.There was no sign of retinal vasculitis. Under increased doses of imunosuppressive treatment, the patient's evolution was characterised by thermic lysis, a better general condition, an improvement of arthralgies and a slow decrease in CRP (9,5 mg/dl at the 35th day after admission) (figure 1). However, the ocular symptoms persisted. Different elements led us to reconsider the diagnosis of Behçet's disease: absence of buccal aphtosis, granulomatous uveitis without vasculitis which does not respond to immunosuppressors, very high inflammatory parameters non consistent with a non-infectious inflammatory disease. The clinical differential diagnosis in the case of our patient, presenting with chronic bilateral uveitis accompanied by sacralgiae and pyrexia is showed in table 2(9).

The presence of increased tracer uptake by the duodenum on (18)F-FDG-PET/CT led us to evoke, among others, the diagnosis of Whipple's disease. Oesogastroduodenoscopy was then performed and showed plaques of villus atrophy in the lower duodenum. Histological examination with PAS staining of the duodenal mucosa revealed neither macrophagic infiltration nor the presence of micro-organisms. No PCR was performed on the duodenal biopsies. Given the diagnostic uncertainty and an atypical uveitis with poor evolution, an anterior ocular chamber tap was performed. PCR for *CMV, HSV1*, *HSV2, toxoplasma, VZV* and *EBV* on the aqueous humour were all negative but PCR for *Tropheryma whippelii* DNA was positive (Bacteriological Laboratory, Lyon Civil Hospices, Dr Yvonne Brun). The PCR for *Tropheryma whippelii* was also positive in blood. Whipple's disease was finally diagnosed. The patient was treated with ceftriaxone IV for 10 days, followed by treatment with trimethoprim-sulfamethoxazol at 160/800 mg twice daily. When methylprednisolone daily doses were decreased, the patient complained of more severe arthralgies. Due to a renewed increase in CRP after 2 months of treatment, trimethoprim-sulfamethoxazole was increased to 3 tablets a day. On follow-up, the right pulmonary nodule had completely disappeared at 4 months. It took 8 months for the CRP and VS to reach normal levels. Trimethoprim-sulfamethoxazol was discontinued after 1 year. Today, 9 months after treatment was discontinued, there is no evidence of relapse: visual acuity is 10/10, arthralgias had disappeared and CRP value is normal (figure 1).

Table 2. Differential diagnosis for clinical presentation with fever, uveitis, spondylarthralgia (adaptad from reference 9)

Inflammatory aetiologies:	Infectious aetiologies:
Ankylosing spondylitis	Syphilis
Psoriatic arthritis	Tuberculosis
Reactive arthritis	Whipple disease
Inflammatory bowel disease	Atypical mycobacteria
Behçet's disease	Brucellosis
Sarcoïdosis	Cat scratch disease
Multiple sclerosis	Leprosy
Systemic lupus erythematosis	Leptospirosis
Wegener's granulomatosis	Lyme disease
	Hepatitis C
	Toxocariasis
	Cysticercosis
	Masquerade syndrome
	Lymphoma

DISCUSSION

Whipple's disease is a rare infectious disease, caused by an actinomycete, *Tropheryma whippelii*. Immune dysfunction factors are also evoked in the pathogenesis. Its ubiquitous presence is documented by the fact that *Tropheryma whippelii* DNA is detected in gastric fluid or duodenal biopsies in more than 10% of people with no clinical signs and in the saliva of more than 30% of healthy individuals[10]. The classic symptoms are diarrhoea, weight loss and arthralgias but the disease may in fact affect any organ and therefore appears with very variable and atypical symptoms, making diagnosis difficult and delayed. The diagnostic methods have evolved. Optical microscopy reveals periodic acid-schiff (PAS) granulations in the macrophages. Electron microscopy shows a typical rod-shaped bacillus with trilamellar membrane. In 1992, the bacteria responsible for Whipple's disease was characterised at molecular level by amplification of its 16S rRNA gene. PCR allows diagnosis in much more cases. *Tropheryma whippelii* culture is still in the experimental phase. Serological tests are still in development.

ORIGINALITY OF THE CASE AND COMPARISON WITH THE LITERATURE

Method : Medline search selecting letters, meta-analysis and review articles, using the key words Whipple's disease, vitreous AND Whipple's disease, vitrectomy AND Whipple's disease.

1. Epidemiology

Whipple's disease is rare. Epidemiology is evolving over time. Between 1907 and 1987, 696 patients were reported (an annual incidence of 8 cases). Since 1980, the incidence has been about 30 reported cases a year. Approximately 363 cases have been published since 1991. The annual incidence in Switzerland is supposed to be 4,5 cases for a population of 7 million inhabitants. The gender ratio is approximately 8 men to 2 women but there is a trend towards an increasing incidence in women(2). As in the case of our patient, the average age at the time of diagnosis is the early fifties in most cases.

2. Clinical presentation

In the 52 cases reported by Durand et al (11), at the time of diagnosis, 90% of patients had general symptoms, 85% had diarrhoea, 83% articular symptoms, 21% neurological manifestations, 17% cardiovascular signs, 13% pleuropulmonary signs, and 15% hyperpigmentation. Only 1 patient out of 52 presented with bilateral sacroiliitis, one patient presented anterior uveitis and another panuveitis. A review by Dutly and Altweg[10] reports ocular symptoms in 5% of cases. There have been approximately 77 cases of ocular Whipple disease published in the literature since 1907 (12).

The delay in diagnosis is often long and depends on the symptoms. For our patient, the delay between the onset of the symptoms in Brazil and the diagnosis was approximatively 24 months. In the series of Durand et al(11) the average delay was 43 months (ranging from 1 month to 30 years). In atypical forms, erroneous diagnoses of seronegative arthritis, ankylosing spondylitis, sarcoidosis, Still's disease and even cerebral lymphoma have been evoked. Immunosuppressive treatment was thus prescribed in many patients making it possible to observe the influence of this treatment on the clinical course of Whipple's disease. Mahnel et al (13) report the early onset of diarrhoea in patients with immunosuppressive treatment. Deeren et al (14) report partial remission of Whipple's disease with corticosteroids, prescribed for a supposed diagnosis of sarcoidosis. In our patient, the immunosuppressive therapy was not associated with diarrhoea or with an aggravation of the symptoms (except perhaps for the ocular signs). We observed an improvement of the arthralgias.Our patient presented a CRP at 34 mg/dl under treatment by methylprednisolone and cyclosporine. An increase of methylprednisolone daily dose and introduction of methotrexate and salazopyrine was followed by a decrease in CRP level and a thermic lysis, which seems unexpected for an infectious disease. The reason is probably that the synthesis of CRP is more inhibited by immunosuppressive therapy than stimulated by *Tropheryma whippelii* who is thought to be an organism of low pathogenicity.

The highest CRP value reported for a case of Whipple's disease is 16 mg/dl in a patient under methotrexate for a misdiagnosis of seronegative spondylarthropathy(15). The high inflammatory parameters of our patient are thus atypical for Whipple's disease. However, this fact led us to suspect an infectious disease.

3. Diagnosis

In case of clinical suspicion of Whipple's disease, the diagnosis must be confirmed by histopathology on tissue biopsies. Even in the absence of gastrointestinal signs, the gold standard is the combination of PAS staining and PCR assay on jejunal biopsy. The literature reports positive histology of biopsies of colon, liver (1 case), brain, kidney, heart valve and positive PCR for *Tropheryma whippelii* on ascitic fluid, cerebrospinal liquid and vitreous(12,16).

Our patient had PCR positive for *Tropheryma whippelii* on blood.

Identification of *Tropheryma whippelii* in the blood is, however, rarely reported. Lowsky et al[17]describe the cases of 2 splenectomised patients with atypical symptoms of Whipple's disease whose blood smears showed bacilli adhered to the erythrocytes. PCR carried out a few years later allowed these bacilli to be identified as *Tropheryma whippelii*. In the series of 5 cases of Whipple's endocarditis from Aïouaz et al (18), PCR was carried out on blood from 3 patients and was positive in 1 of the 3. In patients without endocarditis, not enough cases of PCR for *Tropheryma whippelii* have been performed on blood to determine if it is rare and linked to a state of immunosuppression or if it occurs more often but remains underdiagnosed. In the latter case, PCR on blood could become a diagnostic tool which is less invasive than biopsy.

Our patient also had had a PCR positive for *Tropheryma whippelii* on aqueous humour, which has to our knowledge never been reported before. We found 77 cases

of ocular Whipple disease reported in the literature and only 5 have been diagnosed by PCR on a vitreous sample (12).

As mentioned above, *Tropheryma whippelii* is suspected to be ubiquitous and PCR is positive in gastric

fluid, duodenal biopsies and saliva of some asymptomatic people. However, in our patient, the PCR was positive on blood and aqueous humour, 2 "aseptic" fluids. That means that *Tropheryma whippelii* is pathogen in this case.

Others techniques than histology and PCR can contribute to the diagnosis of Whipple's disease. In case of our patient, PET/CT had helped us in the diagnosis. Radiolabelled leukocytes are not expected to accumulate in the lesions of Whipple because the physiopathology implicates macrophages and not neutrophils. In contrast, (18)F- fluorodesoxyglucose accumulates in inflammatory lesions of Whipple.

4. Treatment

The recommended treatment is an initial treatment with ceftriaxone for 15 days followed by trimethoprim-sulfamethoxazole twice a day for 1 to 2 years. This regimen results in the fewest relapses, particularly with regard to the central nervous system because these drugs are able to cross the blood-brain barrier.Treatment with interferon gamma combined with antibiotherapy could further reduce the number of relapses(10). Fenollar et al(19) suggest using a treatment with doxycycline and hydroxychloroquine in patients with Whipple disease without neurologic involvement. In patients with neurologic involvement, they suggest adding sulfamethoxazole to doxycycline and hydrochloroquine.

CONCLUSIONS

This case report illustrates the difficulty of diagnosing an atypical Whipple's disease. Whipple's disease must be evoked in differential diagnosis of isolated atypical signs of any organs and of systemic inflammatory disease.

High levels of inflammatory parameters must always lead to suspect an infectious aetiology (1). Regression of CRP and a temporary clinical partial remission under immunosuppressive therapy does not mean that the pathology is of inflammatory origin (20).

In all cases of uveitis with atypical signs and/or not responding to the treatment, the internist, in collaboration with the ophthalmologist, must consider to perform an analysis of the ocular fluids, aqueous humour or vitreous.

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