Whipple's disease
A classic case report and review of the literature

R. Vangoitsenhoven[1], J. Nijs[2], H. Verbrugge[3], J. Van Meerbeek[4], L. Van den Bergh[2]

(1) Medical student, KULeuven ; (2) Division of Gastroenterology ; (3) Division of Nephrology ; (4) Division of Pathology, Sint-Trudo Hospital, Sint-Truiden, Belgium.

Abstract

We report the case of a 43-year old carpenter with abdominal complaints and progressive weight loss. The HLA-B27 positive male had been suffering migratory arthropathy for five years, only partially under control with corticosteroids and methotrexate therapy. Endoscopic investigation showed dark staining of the duodenal mucosa and the ileal mucosa had an erythematous aspect with multiple white spots. Abundant periodic acid Schiff - positive macrophages were seen on histologic examination of biopsy samples. This is a classic presentation of Whipple's disease, a rare multisystemic disease caused by the *Tropheryma whipplei*. Typical symptoms are arthropathy, weight loss, abdominal pain and diarrhea, but also systemic and neurological manifestations may occur. The otherwise lethal disease can be treated with long term antibiotics. (Acta gastroenterol. belg., **2010**, 73, **392-396**).

Key words : Whipple's disease, intestinal lipodystrophy, *Tropheryma whipplei*, weight loss, arthropathy, HLA-B27.
Search methods : using the search terms "Whipple's disease", "Whipples disease", "intestinal lipodystrophy" and "*Tropheryma whipplei*" with special interest to additional search terms "HLA" and "immunosuppressant" in PubMed, without date restrictions.

Introduction

Rare diseases are frequently diagnosed improperly, unless they are life-threatening. This was also true for the case of Whipple' disease (WD) we describe below. The patient had suffered some aspecific symptoms for years before an exacerbation led to the correct diagnose. Although WD is extremely rare, it is still very interesting to the clinician because of the broad spectrum of possible symptoms, and from more theoretical point of view because of recent developments in diagnosis and pathogenesis.

Case report

A 43-year old carpenter presented to the gastroenterology department with abdominal pain, nausea, vomiting, diarrhea and weight loss. Over the past six months he had been experiencing an inconvenient feeling and pain in the upper abdomen, uninfluenced by food intake or movement. He reported loss of appetite, nausea and vomiting a few hours postprandially. His stools had varied between normal and diarrhea. There had been a weight loss of 20 kilograms (>15% of body weight) over the past one and a half year, therefrom 5 kilograms in the last month.

He had suffered from gastric ulcers in his twenties. Further relevant medical history consisted of arthropathy in shoulders, elbows, knees and wrists for the past five years, and in neck and back since six months. A single positive rheumatoid factor test was documented but could not be confirmed. The patient had tested positive for histocompatibility antigen-B27 (HLA-B27).

His anti-rheumatic treatment including corticosteroids (6-16 mg/day) and methotrexate (7.5 mg/week) which he had been taking for 13 months, had recently been stopped because of possible effects on his abdominal complaints.

Clinical examination showed a pale and cachectic male without fever. Heart and lung auscultation where normal. On palpation of the abdomen there was pain and reflex rigidity, mainly in the epigastric and suprapubic regions. There was normal peristalsis. There were no lymph nodes palpable, nor any joint abnormalities revealed.

Laboratory findings showed hypochromic microcytic anemia and inflammatory response (Table I).

Table I. — **Laboratory results**

	Unit	At diagnose	After 6 months therapy	Range
Hemoglobin	g/dL	**9.2**	14.3	13.7-17.7
Red blood cells	x10^6/µL	**4.2**	4.8	4.5-5.5
Hematocrit	%	**30**	41	40-50
Mean corpusclar volume	fL RBC	**71.2**	86.4	80.0-100.0
Mean corpusclar hemoglobin	pg/RBC	**21.7**	30.0	27.0-34.0
Mean corpuscular hemoglobin concentration	g/dL RBC	**30.6**	34.7	31.0-36.0
Reticulocytes	x10^3/µL	**12.7**	-	30.0-90.0
Total leucocytes	x10^3/µL	7.2	8.9	4.0-10.0
Neutrofils	%	76.3	56.9	50.0-70.0
Eosinophils	%	4.3	1.0	1.0-6.0
Basophils	%	0.3	0.6	0.0-1.0
Lymphocytes	%	14.7	33.4	20.0-45.0
Monocytes	%	4.4	8.1	5.0-12.0
Platelets	x10^3/µL	**440**	259	150-400
Albumin	g/dL	**2.2**	-	3.5-5.2
Total protein	g/dL	**6.0**	7.5	6.6-8.7
C-reactive protein	mg/dL	**14**	0.2	< 0.50

Correspondence to : Roman Vangoitsenhoven, Kantoorweg 1, 3520 Zonhoven, Belgium. Fax : 011/82.12.33. E-mail : roman.vangoitsenhoven@student.kuleuven.be

Submission date : 03/05/2009
Acceptance date : 22/11/2009

Abdominal ultrasound showed several fluid filled and dilated bowel loops and some ascites in the inferior abdomen. Gastroscopy showed dark staining of the duodenal mucosa (Fig. 1). A mild erythematous aspect of the ileal mucosa with multiple white spots was detected at colonoscopy (Fig. 2).

Histological examination of duodenal and ileal biopsies revealed dilated villi and diffuse infiltration of foamy macrophages in the *lamina propria*. These macrophages turned positive upon periodic acid-Schiff (PAS) staining (Fig. 3). This finding led to the diagnosis of WD.

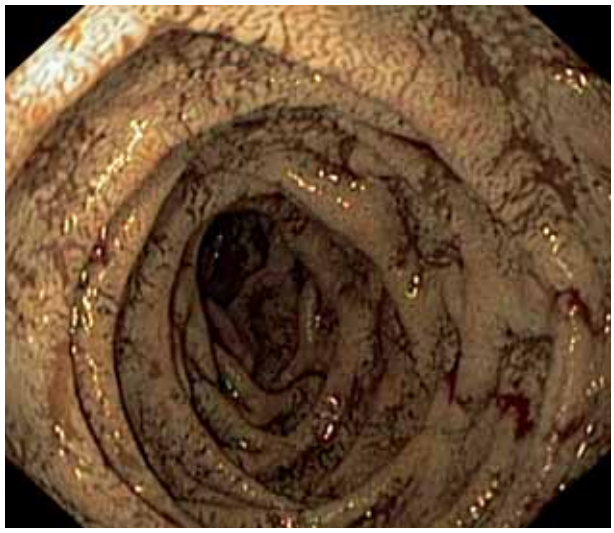

Fig. 1. — Dark staining of the duodenal mucosa.

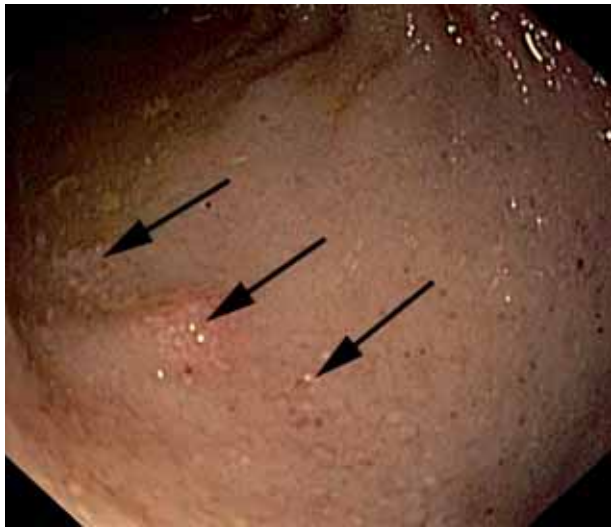

Fig. 2. — White spots (arrows) on the ileal mucosa.

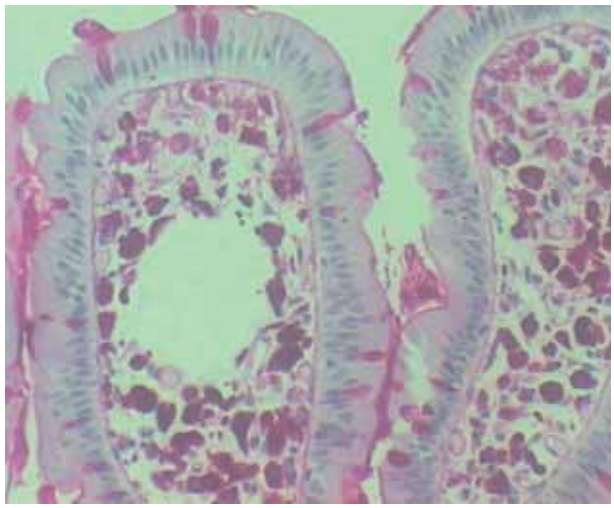

Fig. 3. — PAS-staining highlighted macrophages in the *lamina propria* of duodenal villi (400x).

Discussion

Epidemiology

WD was first described by George Hoyt Whipple, as he discussed "intestinal lipodystrophy" (1). It is a chronic multisystemic infectious disease caused by the *Tropheryma whipplei*, an ubiquitus gram-positive actinomycete (2). The bacterium was successfully cultivated in 2000 (3) and full sequencing of two different strains of its genome was completed in 2003 (4,5). WD is extremely rare, only about 1000 cases have been reported, and it is predominantly diagnosed in white males of Caucasian ancestry at a mean age of 49 years (6). More recent data suggest a larger proportion of female patients (up to 22%) and a rising age at diagnosis (57 years) (7). The observations of a higher incidence in white men, the prevalence of healthy carriers (8-11) and the rarety of the infection hint a genetic predisposition but possible gene defects remain to be revealed.

Clinical manifestations

The cardinal symptoms of classic WD are arthropathy, weight loss, abdominal pain and diarrhea (12). Patients typically have suffered chronic migratory arthralgias, nondeforming oligoarthritis or polyarthritis before they present with other symptoms. The frequently vague articular symptoms precede the actual diagnosis of WD by a mean of 6.7 years (13). Table II presents an overview of most frequent symptoms (14). Note the systemic character of the disease, as there may also be cardiac, pleuropulmonary or mucocutaneous involvement (12,15,16). Neurologic presentation is frequent (10-40%), but very heterogenous in symptomatology. Supranuclear ophtalmoplegia occurs in as many as 32% of the neurological affected patients, but also dementia, psychiatric signs or myoclonus may be provoked by WD (14). Oculomasticatory myorhythmia or oculo-facial-skeletal myorhythmia are considered pathognomonic for WD (12,17).

Pathogenesis

It remains unknown how *T. whipplei* penetrates the human body in general and the central nervous system in specific. The bacterium has been found in various tissues, including cerebrospinal fluid, blood, synovial

Table II. — **Clinical Manifestations of WD (14,27,54)**

Cardinal symptoms	
Weight loss	92%
Diarrhea	76%
Arthralgy	67%
Abdominal pain	55%
Other symptoms	
Lymphadenopathy	60%
Skin hyperpigmentation	45%
Fever	38%
Cardiac manifestation	35-65%
Pulmonary manifestation	35-60%
Neurological manifestation	10-40%
Ocular signs	5-15%
Laboratory findings	
Hypoalbuminemia	91%
Anemia	85%

fluid, skeletal muscle, cardiac valve (18) and in the intestinal mucosa, intracellularly (19,20) or metabolically active extracellularly (21). It seems that WD develops in the combination of preexisting immune deficiency and secondary immune downregulation by the bacterium (22).

Macrophages in WD patients have a reduced expression of CD11b (23) and an impaired ability to degrade intracellular organisms (24). Furthermore, low production of interleukin 12 and reduced levels of interferon gamma inhibit the stimulation of T-helper type 1 cells whereas augmented expression of interleukin 10 stimulates T-helper type 2 lymphocytes (14,22,25-27). In addition, *T. whipplei* replication in macrophages is associated with interleukin 16 expression, which induces macrophage apoptosis (28). It appears that these altered cytokine levels and the subsequent impaired maturation of antigen presenting cells are the cause of WD (14). Although the abnormal cytokine environment, the immune defect appears to be specific to *T. whipplei*, since WD patients do not suffer from opportunistic infections (29).

The hypothesis of underlying genetic predisposition is supported by the reports on family cases (6,30-32). Association between WD and HLA-B27 has also been raised (33,34), but not confirmed (35,36). Martinetti *et al.* claim HLA-DRB1*13 and DQB1*06 alleles occurred significantly more frequently in patients with WD but not in healthy individuals that had been exposed to *T. whipplei* (37).

Diagnosis

Problems in diagnosing WD are probably mainly due to its rarety, but they are also caused by its slow course and the mimicry of many other chronic inflammatory diseases. Upper gastrointestinal endoscopy with at least 5 biopsies of the small intestine is still the diagnostic test of choice (18). Finding of extensive PAS-positive foamy macrophages in the lamina propria and villous atrophy make WD very likely (38,39), and specific antibodies against *T. whipplei* may even improve the diagnostic value of histological examination (40-41). Confirmation can be obtained with electron microscopy where the *T. whipplei* can be identified by its characteristic trilaminar cell wall (6). In modern laboratories the highly sensitive and specific Polymerase Chain Reaction (PCR) technique is probably more easily available. Furthermore, PCR can be used on samples from various tissues such as duodenal biopsies, saliva and cerebrospinal fluid (18,42). Because of many technical pitfalls and possible false-positive results in healthy carriers or due to related bacteria (43), PCR is not suitable for screening and it should only be used for patients with suspicion of WD (14). The same applies to serologic markers : due to low specificity IgM or IgG antibodies provide no useful clinical information (3,44).

Treatment

WD was fatal in the pre-antibiotic era (45). It is essential that treatment must be with antibiotics that are able to cross the blood-brain barrier (46,47) and is continued long enough in order to prevent relapse as well as neurologic symptoms. A good response concerning the extra-neurological signs is mostly apparent in 7 to 21 days (12). Response of neurological symptoms is poor and relapse risk is real (12,46,48). Association of immunomodulatory drugs has been proposed for severe cases : additional treatment with corticosteroids can be beneficial and possibly lifesaving for patients with persistent fever or central nervous system manifestations with cerebral lesions (14) and there has been one report of successful treatment with interferon gamma for recurrent central nervous system disease (49).

Influence of immunosuppressive therapy on WD

As noted above, immunomodulatory drugs like corticosteroids or interferon g may have their benefits in treating WD. But problems may arise when immunosuppressants are given before the infectious disease is recognized. It is not unlikely that undiagnosed patients get immunosuppressive therapy for their arthralgias as these are frequently used for rheumatic complaints. Mahnel and coworkers reported that immunosuppressive therapy is associated with the onset of diarrhea (50). Knowing that the appearance of gastrointestinal complaints often leads to the diagnosis of WD (50,51), one might state that initiation of immunosuppressive therapy can thus indirectly contribute to obtaining the diagnosis. But, we should be aware that these drugs can transform the disease from subacute to life-treathening (52,53).

As long as the pathogenesis is uncompletely understood, one should also consider that it is possible that immunosuppressants make a patient more susceptible for the *Tropheryma whipplei*, and that it is due to an iatrogenic suppressed immune system that the bacterium can actually infect its host.

However, seen the extremely low prevalence of the disease, and the lack of a cheap, patient friendly and reli-

able test, screening every patient with arthralgias before administration of immunosuppressants seems unrealistic.

Outcome

Our patient received initial parenteral therapy of ceftriaxone 2 g once a day during 14 days by daily visit to the hospital. This was followed by oral maintenance therapy with co-trimoxazole (sulfamethoxazol 800 mg + trimethoprim 160 mg) twice a day. The patient's response to treatment was prompt : he was relieved from his abdominal complaints in a few days, quickly regained weight and recovered completely. Control blood examination after 6 months showed normal results (Table I). Interestingly, on further questioning the patient reported a partial relief of the symptoms during sporadic antibiotic treatment for upper respiratory tract infections.

Conclusion

WD is a rare infectious disease with many possible clinical manifestations. It should certainly be considered in a patient with migratory arthropathy, abdominal complaints and weight loss. Although diagnostic techniques and succesful treatment are available, further attention to epidemiology and research on therapeutic regimens and genetic influences is desired.

References

1. WHIPPLE G.H. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. *Bull. Johns Hopkins Hosp*., 1907, **18** : 382.
2. MARTH T., RAOULT D. Whipple's disease. *Lancet*, 2003, **361** : 239-46.
3. RAOULT D., BIRG M.L., LA SCOLA B., FOURNIER P.E., ENEA M., LEPIDI H., ROUX V., PIETTE J.C., VANDENESCH F., VITAL-DURAND D., MARRIE T.J. Cultivation of the bacillus of Whipple's disease. *N. Engl. J. Med*., 2000, **342** : 620-5.
4. BENTLEY S.D., MAIWALD M., MURPHY L.D., PALLEN M.J., YEATS C.A., DOVER L.G., NORBERTCZAK H.T., BESRA G.S., QUAIL M.A., HARRIS D.E., VON HERBAY A., GOBLE A., RUTTER S., SQUARES R., SQUARES S., BARRELL B.G., PARKHILL J., RELMAN D.A. Sequencing and analysis of the genome of the Whipple's disease bacterium Tropheryma whipplei. *Lancet*, 2003, **361** : 637-44.
5. RAOULT D., OGATA H., AUDIC S., ROBERT C., SUHRE K., DRANCOURT M., CLAVERIE J.M. Tropheryma whipplei Twist : a human pathogenic Actinobacteria with a reduced genome. *Genome Res*., 2003, **13** : 1800-9.
6. DOBBINS W.O. III. Whipple's disease. Springfield, IL : Thomas,1987.
7. VON HERBAY A., OTTO H.F., STOLTE M., BORCHARD F., KIRCHNER T., DITTON H.J., MAIWALD M. Epidemiology of Whipple's disease in Germany. Analysis of 110 patients diagnosed in 1965-95. *Scand. J. Gastroenterol*., 1997, **32** : 52-57.
8. EHRBAR H.U., BAUERFEIND P., DUTLY F., KOELZ H.R., ALTWEGG M. PCR-positive tests for Tropheryma whippelii in patients without Whipple's disease. *Lancet*, 1999, **353** : 2214.
9. STREET S., DONOGHUE H.D., NEILD G.H. Tropheryma whippelii DNA in saliva of healthy people. *Lancet*, 1999, **354** : 1178-79.
10. AMSLER L., BAUERNFEIND P., NIGG C., MAIBACH R.C., STEFFEN R., ALTWEGG M. Prevalence of Tropheryma whipplei DNA in patients with various gastrointestinal diseases and in healthy controls. *Infection*, 2003, **31** : 81-85.
11. SCHONIGER-HEKELE M., PETERMANN D., WEBER B., MULLER C. Tropheryma whipplei in the environment : survey of sewage plant influxes and sewage plant workers. *Appl. Environ. Microbiol*., 2007, **73** : 2033-35.
12. DURAND D.V., LECOMTE C., CATHEBRAS P., ROUSSET H., GODEAU P. Whipple disease. Clinical review of 52 cases. The SNFMI Research Group on Whipple Disease. Societe Nationale Francaise de Medecine Interne. *Medicine* (Baltimore), 1997, **76** : 170-84.
13. PUÉCHAL X. Whipple disease and arthritis. *Curr. Opin. Rheumatol*., 2001, **13** : 74-9.
14. SCHNEIDER T., MOOS V., LODDENKEMPER C., MARTH T., FENOLLAR F., RAOULT D. Whipple's disease : new aspects of pathogenesis and treatment. *Lancet Infect. Dis*., 2008, **8** : 179-90.
15. RIEMER H., HAINZ R., STAIN C., DEKAN G., FELDNER-BUSZTIN M., SCHENK P., MÜLLER C., SERTL K., BURGHUBER O.C. Severe pulmonary hypertension reversed by antibiotics in a patient with Whipple's disease. *Thorax*, 1997, **52** : 1014.
16. ELKINS C., SHUMAN, T.A., PIROLO, J.S. Cardiac Whipple's disease without digestive symptoms. *Ann. Thorac. Surg.*, 1999, **67** : 250.
17. LOUIS E.D., LYNCH T., KAUFMANN P., FAHN S., ODEL J. Diagnostic guidelines in central nervous system Whipple's disease. *Ann. Neurol*., 1996, **40** : 561-68.
18. FENOLLAR F., PUECHAL X., RAOULT D. Whipple's disease. *N. Engl. J. Med*., 2007, **356** : 55-66.
19. RAOULT D., LA SCOLA B., LECOCQ P., LEPIDI H., FOURNIER P.E. Culture and immunological detection of Tropheryma whippelii from the duodenum of a patient with Whipple disease. *JAMA*, 2001, **285** : 1039-43.
20. RAOULT D., LEPIDI H., HARLE J.R. Tropheryma whipplei circulating in blood monocytes. *N. Engl. J. Med*., 2001, **345** : 548.
21. FREDRICKS D.N., RELMAN D.A. Localization of Tropheryma whippelii rRNA in tissues from patients with whipple's disease. *J. Infect. Dis*., 2001, **183** : 1229-37.
22. MARTH T., NEURATH M., CUCCHERINI B.A., STROBER W. Defects of monocyte interleukin 12 production and humoral immunity in Whipple's disease. *Gastroenterology*, 1997, **113** : 442-8.
23. MARTH T., ROUX M., VON HERBAY A., MEUER S.C., FEURLE G.E. Persistent reduction of complement receptor 3 alpha-chain expressing mononuclear blood cells and transient inhibitory serum factors in Whipple's disease. Clin. *Immunol. Immunopathol*., 1994, **72** : 217-26.
24. BAI J.C., SEN L., DIEZ R., NIVELONI S., MAURIÑO E.C., ESTEVEZ M.E., BOERR L.A. Impaired monocyte function in patients successfull treated for Whipple's disease. *Acta Gastroenterol. Latinoam*., 1996, **26** : 85-89.
25. ECTORS N., GEBOES K., DE VOS R., HEIDBUCHEL H., RUTGEERTS P., DESMET V., VANTRAPPEN G. Whipple's disease : a histological, immunocytochemical and electronmicroscopic study of the immune response in the small intestinal mucosa. *Histopathology*, 1992, **21** : 1-12.
26. MARTH T., KLEEN N., STALLMACH A., RING S., AZIZ S., SCHMIDT C., STROBER W., ZEITZ M., SCHNEIDER T. Dysregulated peripheral and mucosal Th1/Th2 response in Whipple's disease. *Gastroenterology*, 2002, **123** : 1468-77.
27. DESNUES B., IHRIG M., RAOULT D., MEGE J.L. Whipple's disease : a macrophage disease. CLIN. VACCINE IMMUNOL., 2006, **13** : 170-78.
28. BENOIT M., FENOLLAR F., RAOULT D., MEGE J.L. Increased levels of circulating IL-16 and apoptosis markers are related to the activity of Whipple's disease. *PLoS ONE*, 2007, **6** : e494.
29. LAMMAS D.A., DE HEER E., EDGAR J.D., NOVELLI V., BEN-SMITH A., BARETTO R., DRYSDALE P., BINCH J., MACLENNAN C., KUMARARATNE D.S., PANCHALINGAM S., OTTENHOFF T.H., CASANOVA J.L., EMILE J.F. Heterogeneity in the granulomatous response to mycobacterial infection in patients with defined genetic mutations in the interleukin 12-dependent interferon-gamma production pathway. *Int. J. Exp. Pathol*., 2002, **83** : 1-20.
30. GROSS J.B., WOLLAEGER E.E., SAUER W.G., HUIZENGA K.A., DAHLIN D.C., POWER M.H. Whipple's disease, report of four cases, including two in brothers, with observations on pathological physiology, diagnosis, and treatment. *Gastroenterology*, 1959, **36** : 65-93.
31. DYKMAN D.D., CUCCHERINI B.A., FUSS I.J., BLUM L., WOUTERS R.S. Whipple's disease in a father-daughter pair. *Dig. Dis. Sci*., 1999, **44** : 2542-4.
32. PONZ DE LEON M., BORGHI A., FERRARA F., CONTRI M., RONCUCCI L. Whipple's disease in a father-son pair. *Inter. Emerg. Med*., 2006, **1** : 254-6.
33. MARTH T., KLEEN N., STALLMACH A., RING S., AZIZ S., SCHMIDT C., STROBER W., ZEITZ M., SCHNEIDER T. Dysregulated peripheral and mucosal Th1/Th2 response in Whipple's disease. *Gastroenterology*, 2002, **123** : 1468-77.
34. DOBBINS W.O. III. HLA antigens in Whipple's disease. *Arthritis Rheum*., 1987, **30** : 102-5.
35. BAI J.C., MOTA A.H., MAURIÑO E., NIVELONI S., GROSSMAN F., BOERR L.A., FAINBOIM L. Class I and class II HLA antigens in a homo-

geneous Argentinian population with Whipple's disease : lack of association with HLA-B 27. *Am. J. Gastroenterol*., 1991, **86** : 992-4.
36. OLIVIERI I., BRANDI G., PADULA A., DI STEFANO M., MANTOVANI W., CALABRESE C., SACCOCCIO G., DI FEBO G., CORAZZA G.R., MIGLIOLI M., BIASCO G. Lack of association with spondyloarthritis and HLA-B27 in Italian patients with Whipple's disease. *J. Rheumatol*., 2001, **28** : 1294-7.
37. MARTINETTI M., BIAGI F., BADULLI C., FEURLE G.E., MÜLLER C., MOOS V., SCHNEIDER T., MARTH T., MARCHESE A., TROTTA L., SACHETTO S., PASI A., DE SILVESTRI A., SALVANESCHI A., CORAZZA G.R. The HLA alleles DRB1*13 and DQB1*06 are associated to Whipple's disease. *Gastroenterology*, 2009, **136** : 2289-94.
38. GEBOES K., ECTORS N., HEIDBUCHEL H.P., RUTGEERTS P.J., DESMET V.J., VANTRAPPEN G.R. Whipple's disease : the value of upper gastrointestinal endoscopy for the diagnosis and follow-up. *Acta Gastroenterol. Belg*., 1992, **55** : 209-19.
39. MÖNKEMÜLLER K., FRY L.C., VON ARNIM U., NEUMANN H., EVERT M., MALFERTHEINER P. Whipple's disease : an endoscopic and histologic study. *Digestion*, 2008, **77** : 161-5.
40. BAISDEN B.L., LEPIDI H., RAOULT D., ARGANI P., YARDLEY J.H., DUMLER J.S. Diagnosis of Whipple disease by immunohistochemical analysis : a sensitive and specific method for the detection of Tropheryma whipplei (the Whipple bacillus) in paraffin-embedded tissue. *Am. J. Clin. Pathol*., 2002, **118** : 742-48.
41. LEPIDI H., FENOLLAR F., GEROLAMI R., MEGE J.L., BONZI M.F., CHAPPUIS M., SAHEL J., RAOULT D. Whipple's disease : immunospecific and quantitative immunohistochemical study of intestinal biopsy specimens. *Hum. Pathol*., 2003, **34** : 589-96.
42. FENOLLAR F., RAOULT D. Molecular techniques in Whipple's disease. *Expert Rev. Mol. Diagn*., 2001, **1** : 299-309.
43. ROLAIN J.M., FENOLLAR F., RAOULT D. False positive PCR detection of Tropheryma whipplei in the saliva of healthy people. *BMC Microbiol*., 2007, **7** : 48.
44. MORGENEGG S., MAIBACH R., CHAPERON D.N., HERZOG K., ALTWEGG M. Antibodies against recombinant heat shock protein 65 of Tropheryma whipplei in patients with and without Whipple's disease. *J. Microbiol. Methods*, 2001, **47** : 299-306.
45. PAULLEY J.W. A case of Whipple's disease (intestinal lipodystrophy). *Gastroenterology*, 1952, **22** : 128-33.
46. KEINATH R.D., MERREL D.E., VLIETSTRA R., DOBBINS W.O. III. Antibiotic treatment and relapse in Whipple's disease. Long-term follow-up of 88 patients. *Gastroenterology*, 1985, **88** : 1867-73.
47. FEURLE G.E., MARTH T. An evaluation of antimicrobial treatment for Whipple´s disease. Tetracycline versus Trimethoprim-Sulfamethoxazole. *Dig. Dis. Sci*., 1994, **39** : 1642-8.
48. SCHNIDER P.J., REISINGER E.C., GERSCHLAGER W., MÜLLER C., BERGER T., KREJS G.J., AUFF E. Long-term follow-up in cerebral Whipple's disease. *Eur. J. Gastroenterol. Hepatol*., 1996, **8** : 899-903.
49. SCHNEIDER T., STALLMACH A., VON HERBAY A., MARTH T., STROBER W., ZEITZ M. Treatment of refractory Whipple disease with interferon-γ. *Ann. Intern. Med*., 1998, **129** : 875-7.
50. MAHNEL R., KALT A., RING S., STALLMACH A., STROBER W., MARTH T. Immunosuppressive therapy in Whipple's disease patients is associated with the appearance of gastrointestinal manifestations. *Am. J. Gastroenterol*., 2005, **100** : 1167-73.
51. VANDERSCHUEREN D., DEQUEKER J., GEBOES K. Whipple's disease in a patient with longstanding seronegative polyarthritis. *Scand. J. Rheumatol*., 1988, **17** :4 23-6.
52. LAMPARTER S., DITTRICH C., KOEHLER H.H. Exacerbation of Whipple disease by immunosuppressants. *J. Clin. Gastroenterol*., 2008, **42** : 760-1.
53. KREMER A.E., BUDENHOFER U., BEUERS U., RUST C. 47-jähriger Hundezüchter mit chronischer Polyarthritis, Gewichtsverlust und hohem Fieber. *Z. Gastroenterol*., 2008, **46** : 431-4.
54. SCHALLER J., CARLSON J.A. Erythema nodosum-like lesions in treated Whipple's disease: signs of immune reconstitution inflammatory syndrome, *J. Am. Acad. Dermatol*., 2009, **60** : 277-88.