Introduction

The Whipple’s Disease (W.D.) is a multisystemic, chronic infectious disease, very rare, with an annual incidence of 1 per 1,000,000 inhabitants (1) affecting mainly male patients 40-50 years old (2), described by Wipple for the first time in 1907 (3). The etiology was attributed to Gram-positive Actinomycete namely the Tropheryma Whipplei (T.W.) observed and identified 100 years after description of the disease, when the rod-shaped organisms were observed inside the macrophages and in the cytoplasm vacuoles of various cellular elements, such as those of the duodenal mucosa and other tissues (4-6).

The symptoms of W.D. are multisystemic with initial predominant involvement of the joints followed by, or concurrent with, the involvement of gastrointestinal system with onset of diarrhea, weight loss and malabsorption (7). W.D. can sometimes also affect the myocardial cells with endocarditis (8), or associated with different neurological symptoms, accompanied by psychic disturbances. Prolonged antibiotic treatment with trimethoprim and sulfamethoxazole continuously for 1-2 years guarantees the remission of the disease and prevents relapse (9). The Authors describe a rare case of W.D. treated with emergency surgical procedure for bowel obstruction and perforation.

Case report

P.D. a 56 years old woman admitted for emergency bowel obstruction with severe cachexia, malabsorption and dilated cardiomyopathy, associated with cyclic bloodstained diarrhoea, with weight loss and psychiatric disorders. Her medical history revealed a previous hospitalization for deep vein thrombosis (DVT) of the left leg.
while the CT of the abdomen showed edema with thickening of the intestinal wall with swelling at the level of ileus. Following the worsening of malabsorption with accentuated organic decay, the patient was subjected to further CT scan which confirmed thickening of the intestinal wall of the small intestine, while PET noted a diffuse accumulation of the radioisotope on the intestinal wall, particularly in the small pelvis.

The CT performed during emergency hospitalization in our Department showed a diffuse dilatation of the entire small intestine, with numerous levels and gastrorectasia associated to mesenteric lymphadenopathy and thickened intestinal loops. Exploratory laparotomy confirmed the intestinal obstruction and concomitant suppurative peritonitis, with thickened bowel loops conglomerated and widespread edema of the mesentery. In relation to the clinical conditions and the running peritonitis, an ileostomy and biopsy of the wall of intestine and of lymph nodes were performed, which histologically showed numerous macrophages, with intracellular PAS-positive material. Given these findings, the diagnosis of W.D. was assumed. Appropriate antibiotic therapy (Trimethoprim and Sulfomethoxazole) and parenteral nutrition was scheduled.

The echocardiogram noted a dilated cardiomyopathy with dilatation of left ventricular wall and moderate hypokinesia and mitro-tricuspid insufficiency.

Forty-five days after admission the patient was discharged in good hemodynamic compensation with antibiotic therapy at full dosage.

Discussion

The rarity of W.D. and the difficulty of early diagnosis pose some questions of discussion particularly in view of the case observed. Males are more affected, but our patient was a woman (1). The onset of disease has been characterized by psychic disorders and subsequently associated to gastrointestinal disorders. This psychiatric manifestations initially generated an incorrect clinical diagnosis with predominant focus on anorexia. In fact psychic and neurological symptoms haven been reported in literature in 15-60% (2,3,9-11), with cases of ophthalmoplegia, nystagmus, sleep patterns, ataxia and also coma (33 %) and death from irreversible brain damage or atrophy, with findings of T.W. in the cerebrospinal fluid (12). Although the symptoms are diversified cognitive manifestations prevail such as dementia, memory loss and ophthalmoplegia (11-13).

The common and more frequent symptoms involve the gastrointestinal system (75-95%) (1,3,14), with weight loss, diarrhea, abdominal pain, whose pathophysiology is due to bacterial overgrowth inside of the intestinal wall and mucosa with diffuse edema, exudates and mesenteric lymphadenopathy which can evolve to chronic constipation until extreme intestinal obstruction (15). The mesenteric and retroperitoneal lymphadenopathy which can aggravate the lymphatic stasis and edema of the intestinal mucosa which is the cause of malabsorption and diarrhea. The lamina propria is expanded, with widespread deposits of lipids up to lipodystrophy, and in-
increases the risk of constipation in advanced stages of the disease (16).

The evolution of the constipation can lead to the mechanical intestinal obstruction, which is rare, and requires a surgical emergency treatment. In these cases, it is suggested a loop ileostomy with subsequent closure only after the complete remission of the disease. The massive widespread of the disease with the diffuse edema of the bowel mucosa does not allow a resection in emergency because of the high risk of dehiscence of the anastomosis and occurrence of fistulas of difficult management. The damage of the intestinal mucosa sometimes is ex-
pressed by the presence of blood in the stool with occult blood or signs of bleeding in the feaces 30% (17).

The polyarthralgia is a common symptom (65-90%) and can be the predominant one. This is a chronic polyarthritis with migrant primary involvement of distal joints and evolutionary tendency towards the spondylosis (9, 15, and 18).

The cardiovascular system is affected to a lesser extent from infectious disease (17-55%) with signs of endocarditis in valvular involvement towards sclerosis of the wall of the valve with prevalent involvement of the mitral valve, which requires its complete replacement (1,8,9,15).

The rare frequency of endocarditis is documented by the presence of blood cultures associated with low notes of inflammation and fever (19).

15% of the patients do not present classic polyisystemic symptoms (20). Although in literature cases are observed where patients are affected from different pathologies as hyperpigmentation, cough, pleurisy, sleep disorders, while the absence of gastrointestinal signs is extremely rare (1,17).

The W.D. mimics others chronic inflammatory diseases, for which the diagnosis is mandatory with researches of degradation products of T.W. inside of the histiocytes of the intestinal mucosa, cerebrospinal fluid, synovial tissue and other cellular structures affected by infection (PAS-positive). The gastrointestinal endoscopy of the small intestine is the first diagnostic test and affords an early diagnosis, which allows the detection of T.W. and the degree of evolution of the disease in relation to lymphatic hyperplasia and lipodystrophy of the intestinal mucosa (21, 22).

Important diagnostic support is provided by the molecular diagnosis with RNA polymerase chain reaction technique (PCR) which gives a determination of the nucleotide sequence of the 16Sr rRNA gene of T.W. This test has a high sensitivity but low specificity with possible finding of false positives associated to patients who are not affected by W.D. and related to the fractions of gene of others actinomycetes. For these reasons the diagnostic test is indicated only in patients with multisystemic characteristic symptoms of W.D. (3). In literature are reported some false negatives (23) as the case described by the Authors. The PCR false positive result arise when different bacterium with 16SrRNA based PCR is used for the first time (24). Diagnostic test RNA polymerase is however important as it allows to evaluate the degree of patient response to antibiotic treatment and guarantees a differential diagnosis of PAS-positive cases associated with other bacteria such as Mycobacterium avium-intracellular, Rhodococcus equi, Cerens Bacillus, Corynebacterium, Histoplasma.

These diagnostic tests (PCR and PAS positive) allow the differentiation with other malabsorption disorders such as celiac disease, Cohn’s disease, lymphoma, the other forms of the amyloidosis, also because these tests should be performed in biopsy of bowel, synovial liquid and cerebrospinal fluid for a complete and detailed diagnosis of W.D. The foamy toyos appearance of macrophages inside the intestinal mucosa determines an extensive involvement of the lamina propria, as observed by Wipple and linked to the proliferation of macrophages developing internally an infectious agent (1). This morphology justifies the etymology of the name "Trophy", from the Greek (food), and "Eryma" (barrier), that literally is "obstacle to absorption of food", with a latency period for the onset of symptoms of six years (9).

The disease is epidemiologically linked to a fecaloral transmission, mostly of male patients which work with animals, but the proportion between female and male is rising, also because of a genetic predisposition or W.D. has been discussed (2).

The clinical evolution towards intestinal obstruction requires antibiotic treatment with Trimethoprim and Sulfamethoxazole, a full dose continued for 1-2 years (1,7,9) or until complete regression of the disease. Treatment with tetracycline revealed cases of recurrence in 40% of patients with neurological symptoms and involvement of CNS (21), whereby for these patients is required an antibiotic therapy with ceftriaxone, 2 grams for 2 weeks, followed by oral cotrimoxazole, 2 times daily for 1-2 years, in consideration of the ability to overcome the blood-barrier of these antibiotics (14). The antibiotic treatment reduces the clinical symptoms, especially diarrhea, fever and malabsorption in 1 week, while the rest of clinical signs tend to decrease in 3-4 weeks. Gastroscopy with duodenal biopsy within 6-12 months from the onset of antibiotic treatment allows a proper follow-up (25).

Conclusions

The W.D. confirms to be a rare multisystemic condition with different clinical onset most frequently affecting the gastrointestinal system (65-90%), the skeleton with arthritis and polyarthralgia of large joints (70 %) and neurological signs (15-20 %).

The gastroscopy with duodenal biopsy is mandatory for the diagnosis of W.D., above all when the gastrointestinal system is involved. The biopsy evidences are: thickening of the intestinal wall, a widened villi, lymphatic occlusion of vessel and lipid deposit in the lamina of the wall, which allows the identification of the bacteria or remnants of bacteria in the foamy macrophages with vesicles PAS-positive. The differential diagnosis with others intestinal infections (Mycobacterium avium, corynebacterium, Rhococcus and so on), which shows
PAS-positive macrophages, is possible using molecular diagnosis with RNA polymerase, which has a higher specificity for the T. W.

The intestinal obstruction requires an emergency surgical treatment with ileostomy for massive swelling and edema of intestinal loops, which do not allow a valid segmental resection. Given the very high risk of fistula in this case, the AA consider also appropriate to proceed to intestinal recanalization only after complete remission of the pathology. The antibiotic treatment of choice is a full parenteral dose for 2 weeks of trimethoprim and sulfomethoxazole in the initial stages of disease, followed by maintenance therapy for 1-2 years or so, until complete remission of clinical signs. Follow-up gastroscopy with duodenal biopsies should be performed after 6-12 months, if the PAS research is negative in the macrophages, antibiotic treatment can be stopped. The treatment with parenteral cefotriaxone followed by oral co-trimoxazole is reserved to the forms with involvement of CNS for the ability of these antibiotics to overcome the blood-brain barrier.

References