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An endoscopic and pathological survey of digestive tract disorders in patients infected with human immunodeficiency virus monitored in the Clinic of Infectious Diseases from Tirgu Mures, Romania

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Abstract

Gastrointestinal symptoms are among the most frequent complaints of patients infected with human immunodeficiency virus (HIV). *Purpose*: An endoscopic and histopathological survey of digestive tract diseases among HIV-infected patients monitored in the Clinic of Infectious Diseases I from Tirgu Mures, Romania. *Materials and Methods*: Retrospective, observational study, on a group of 38 HIV-positive patients admitted to the Clinic of Infectious Diseases I from Tirgu Mures, Romania, during 2006–2013, undergoing upper/lower endoscopy. We collected data regarding the results of endoscopy and histopathological examination, CD4+ T-lymphocytes levels, microbiological examinations and outcome. Statistical analysis, performed by using Microsoft Office Excel 2007 and GraphPad Prism 5 programs, included contingency tables analysis and comparing means. *Results*: Our study depicted a variety of digestive disorders among HIV-infected patients, ranging from opportunistic infections to HIV enteropathy and non-HIV-associated conditions. The presence of *Candida* esophagitis implied significantly lower levels of CD4+ T-cells (p=0.0043). We found a statistically significant negative association between antiretroviral therapy and the presence of opportunistic infections (p=0.0375, OR=0.2030, 95% CI 0.0423–0.9741). Thirteen (34.21%) patients died, mostly due to tuberculosis and central nervous system infections. All were diagnosed with acquired immunodeficiency syndrome (AIDS). *Conclusions*: HIV-infected patients experience a wide variety of digestive tract disorders, both AIDS-defining illnesses and non-HIV-associated conditions. Gastrointestinal opportunistic infections occur more often among patients with low CD4+ T-cells levels and in those not receiving antiretroviral therapy. Although digestive conditions did not represent direct causes of death in our study, they may predict an unfavorable outcome in AIDS-stage patients.

Keywords: human immunodeficiency virus, digestive tract disorders, endoscopy, pathology.

Introduction

The relationship between human immunodeficiency virus (HIV) infection and the digestive tract has represented an important research issue, considering the extension of HIV pandemics. Apart from the initial role played by the gut-associated lymphoid tissue (GALT), including CD4+ T-cells expressing CCR5 co-receptor, in the pathogenesis of primary HIV infection [1–3], the gastrointestinal tract may represent the site of HIV-associated pathology, ranging from various opportunistic infections (OI) and malignant lesions to HIV enteropathy [1, 4]. Several gastrointestinal conditions, including fungal (*Candida*, *Histoplasma capsulatum*), viral (cytomegalovirus, herpes simplex virus), parasitic (*Isospora*, *Cryptosporidium*), bacterial (including *Mycobacterium tuberculosis* and *M. avium* complex) and neoplastic (Kaposi's sarcoma) diseases, along with wasting syndrome, are included in the *United States Centers for Diseases Control and Prevention* (CDC) classification of HIV infection [5].

Over 50% of all HIV-infected patients in all stages have gastrointestinal complaints [2, 4]. Causes range from opportunistic infections and malignant lesions to the effect of HIV alone – HIV enteropathy, non-HIV associated pathology or adverse events to medication prescribed for HIV or associated co-morbidities [2–4, 6–8].

Several researchers [3, 7] have noticed a changing tendency regarding the gastrointestinal pathology in HIV-infected patients, after the initiation of highly active anti-retroviral therapy (HAART), with a decrease in acquired immunodeficiency syndrome (AIDS)-defining diseases and an increase in non-HIV-related disorders, such as peptic ulcer and gastroesophageal reflux disease (GERD) [7], while pre-HAART era was dominated by opportunistic infections and malignancies [9]. However, opportunistic infections are still reported nowadays [10, 11], especially in HAART-naïve patients and late-presenters [2] or at low levels of CD4+ T-lymphocytes [8].

Although stool examination for bacteria, parasites and fungi settles the etiology in about 50% of the cases [1, 12], endoscopy and histopathological examination of biopsy fragments is often necessary to establish the diagnosis [4, 13]. Besides, one must bear in mind the idea that sometimes, in severely immunocompromised patients, more than one etiology might be encountered [4, 9].

The purpose of the present study was to review, from the point of view of endoscopic and histopathological results, the digestive tract disorders encountered among HIV-infected patients monitored in the Clinic of Infectious Diseases I from Tîrgu Mureş, Romania, either undergoing or non-receiving HAART, while correlating their range to the immune status of the subjects.

Materials and Methods

We performed a retrospective, descriptive study, on a group of 38 HIV-infected patients, admitted to the Clinic of Infectious Diseases I from Tîrgu Mureş, department of the Emergency County Hospital, Tîrgu Mureş, Mureş County, Romania, between 2006–2013, who underwent upper/lower digestive endoscopy for gastrointestinal complaints: nausea, vomiting, abdominal pain, diarrhea, weight loss. The specimens obtained by endoscopy were fixed in 10% buffered formalin and then embedded in paraffin blocks. Four-µm tick sections were obtained from the paraffin blocks and stained with Hematoxylin and Eosin (HE).

We collected the subjects' demographic data (age, gender, environment), as well as information regarding the results of endoscopic and histopathological examinations, the patients' immunological and virological status, reflected in the level of CD4+ T-lymphocytes and HIV-RNA plasma viral load and microbiological examinations relevant for diagnosis. The patients' clinical outcome, expressed by their survival rate, was also noted.

Data were processed using Microsoft Office Excel 2007 and GraphPad Prism 5 programs. Statistical analysis included the analysis of contingency tables, by using χ^2 test and calculating odds ratio (OR), as well as the comparison of central tendencies, using Mann–Whitney non-parametric test. We set the level of statistical significance at α=0.05 for a 95% confidence interval (CI).

Results

The studied group was homogenous from the point of view of demographic data: gender distribution – 42.11% males:57.89% females, environment distribution – 42.11% urban:57.89% rural, as well as age features – mean age 23 years, median and mode 21 years, extremes: 17–58 years.

The average level of CD4+ T-lymphocytes was of 283 cells/µL, with a median of 249 cells/µL, mode of 20 cells/µL and extremes of 7–852 cells/µL. Seventeen (44.74%) subjects had CD4+ T-cells levels less than 200 cells/µL. The average HIV-RNA plasma viral load (VL) was 106 314 copies/mL, with a median of 13 719 copies/mL and extremes ranging from undetectable to 1 548 816 copies/mL. The majority of patients – 35 (92.1%) – were in AIDS stage. Sixteen (42.11%) patients were diagnosed with wasting syndrome.

Twenty-two (57.89%) patients were under effective antiretroviral therapy. Sixteen (42.11%) patients received steroidal or non-steroidal anti-inflammatory drugs (NSAIDs), while eight (21.05%) subjects were under anti-tuberculosis therapy.

The main complaints imposing digestive tract endoscopy were abdominal pain – 26 (68.42%) cases, retrosternal pain accompanied by odynophagia – nine (23.68%) cases, lack of appetite – 20 (52.63%) cases, nausea and vomiting – 13 (34.21%), diarrhea – seven (18.42%) cases, weight loss – six (15.79%) cases and rectal bleeding – two (5.26%) cases.

Endoscopic findings included esophageal candidiasis – nine (23.68%) patients, one with mycotic esophageal stenosis (with *Candida albicans* or non-*albicans* strains isolated from oral/pharyngeal swabs in all cases), gastro-esophageal reflux disease (GERD) – five (13.16%) patients, erythematous – nine (23.68%) and erosive antral gastritis – two (5.26%) subjects, as well as atrophic corporeal gastritis or pangastritis – one (2.63%) case each, chronic duodenitis or duodenal ulcer – two (5.26%) cases each, hiatal hernia – three (7.89%) patients and enterogastric reflux gastritis in non-surgical patients – three (7.89%). One patient diagnosed with hepatitis B virus (HBV) infection and subsequent cirrhosis had esophageal varices on endoscopy. Lower endoscopy raised the suspicion of inflammatory bowel disease – ulcerative colitis in one patient (2.63%) and depicted hemorrhoidal disease in two (5.26%) cases with rectal bleeding. Twelve (31.58%) patients did not have any pathological changes on endoscopy. These cases raised the question of psychosomatic disorders or medication adverse events.

Out of the seven cases of diarrhea, two were diagnosed as intestinal cryptosporidiosis based on the detection of *Cryptosporidium parvum* antigen from feces, one with simultaneous stool culture positive for *Shigella dysenteriae* and concomitant diagnosis of *Candida* esophagitis.

Biopsies were collected only in 12 (31.57%) cases and subjected to histopathological examination. Biopsies were contraindicated in many patients due to bleeding risk (thrombocytopenia, coagulation factors deficit) or could not be performed due to patients' lack of cooperation.

Histopathological examination supported endoscopic diagnosis in many cases: esophageal candidiasis (Figure 1), GERD and Barrett's esophagus (Figure 2), antral gastritis, chronic duodenitis (Figure 3).

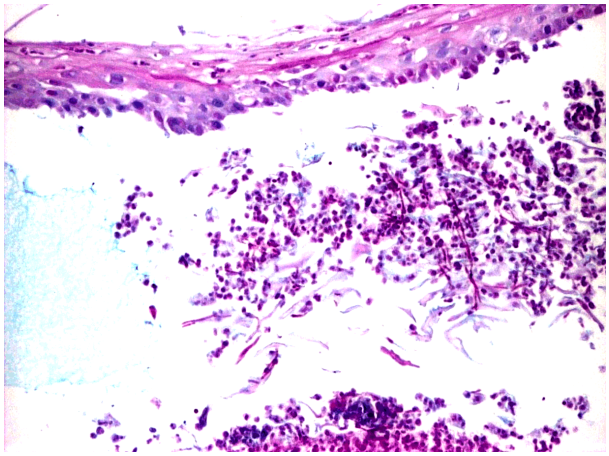


Figure 1 – ***Candida esophagitis (HE staining, ×50).***

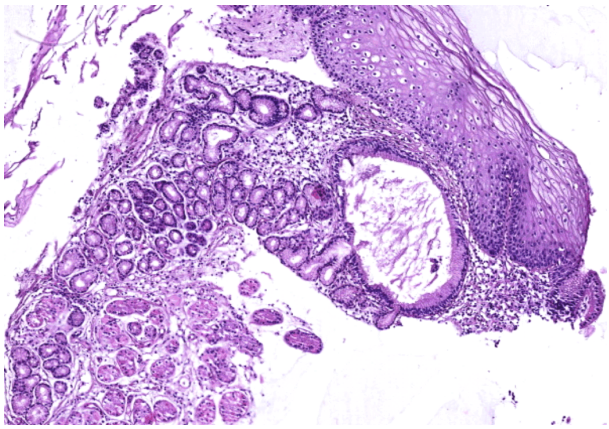


Figure 2 – ***Barrett's esophagus (HE staining, ×50).***

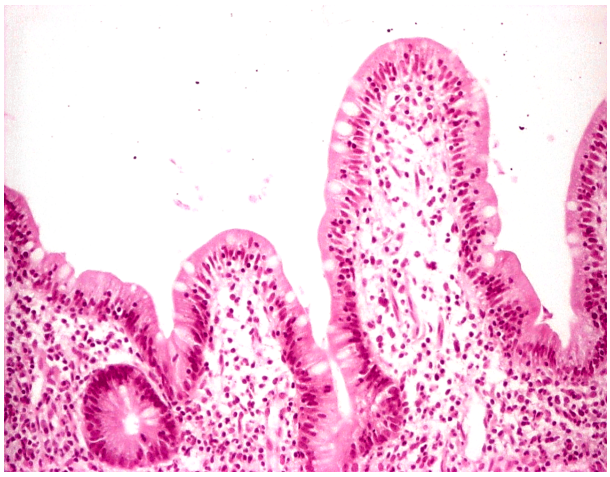
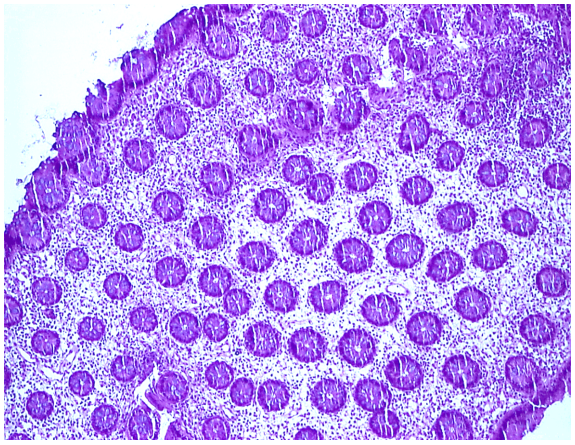
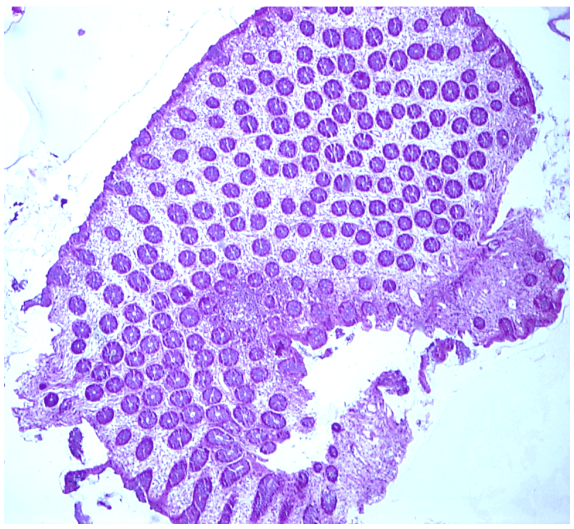


Figure 3 – ***Chronic duodenitis (HE staining, ×50).***

The lack of endoscopic changes, however, did not guarantee the lack of pathology. Histopathological examination revealed villous atrophy, crypt hyperplasia, apoptotic bodies inside epithelial cells, suggestive for HIV enteropathy in diarrheic patients with weight loss and no endoscopic abnormalities (Figure 4, a and b). Besides, focal active colitis on histopathological examination (Figure 5) suggesting infectious etiology of diarrhea was found in two patients with negative stool cultures and endoscopy, but with subsequent favorable outcome under antibiotic treatment.



(a)



(b)

Figure 4 – ***HIV enteropathy – colonic biopsy. HE staining: (a) ×100; (b) ×50.***

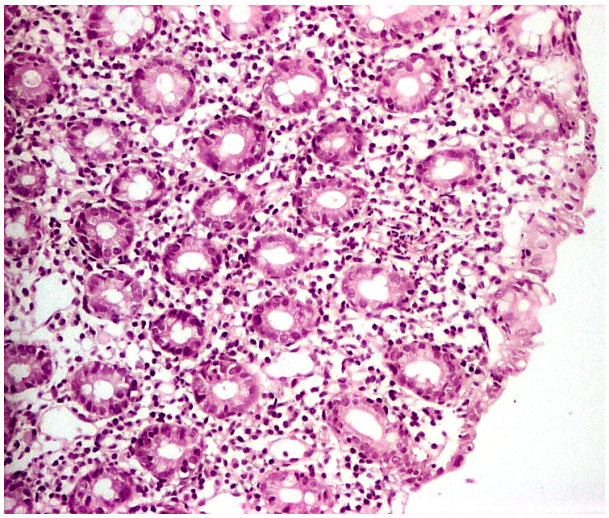


Figure 5 – ***Focal active colitis (HE staining, ×50).***

Eight out of the nine cases of *Candida* esophagitis appeared in severely immunocompromised patients, with CD4+ T-lymphocytes levels less than 200 cells/μL. By performing Mann–Whitney non-parametric test for means comparing, we found that patients with esophageal candidiasis had significantly lower levels of CD4+ T-cells (p=0.0043) compared to those with other digestive illnesses. The mean/median/extreme level of CD4+ T-lymphocytes were 108/22/7–728 cells/μL, compared to 331/280/20–852 cells/μL in patients suffering from other digestive disorders (Figure 6).

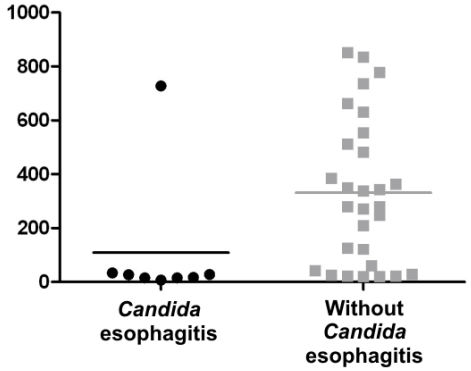


Figure 6 – ***CD4+ T-lymphocytes level (cells/μL) in HIV-positive patients with/without Candida esophagitis.***

Nineteen (86.36%) out of the 22 patients undergoing HAART developed non-AIDS defining illnesses: GERD, erosive/erythematous gastritis, enterogastric reflux gastritis, duodenitis or peptic ulcer. HIV-infected patients without HAART developed gastrointestinal opportunistic infections more frequently (43.75% cases), compared to those under antiretroviral treatment (13.63%). χ^2 test revealed a statistically significant negative association between HAART and the presence of digestive opportunistic infections: p=0.0374, OR=0.2030, 95% CI 0.0423–0.9741 (Figure 7).

Thirteen (34.21%) patients died within the time period of the study, at various intervals of time, one month–two years distance from endoscopic examination. The main causes of death were pulmonary and extrapulmonary TB and central nervous system infections. Digestive disorders did not represent the direct cause of death in these patients.

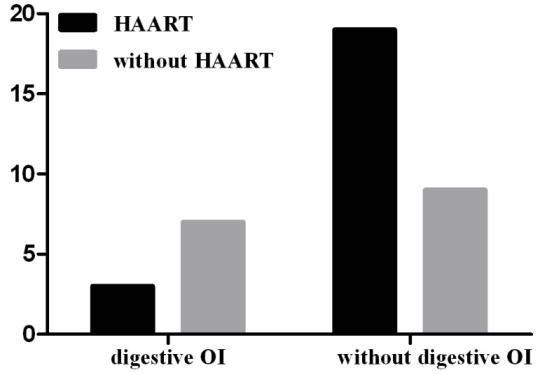


Figure 7 – *Digestive OI and HAART.*

Discussion

According to literature data, 50–70% HIV-infected patients present to hospital with digestive symptoms [2, 4]. Our subjects' main complaints were abdominal pain, lack of appetite, retrosternal pain and odynophagia, nausea, vomiting, diarrhea and weight loss.

A variety of digestive tract disorders were diagnosed, ranging from opportunistic infections, mostly esophageal candidiasis, to HIV enteropathy, as well as non-HIV associated conditions: GERD, acute/chronic gastritis or duodenitis, peptic ulcer, focal active colitis and hemorrhoidal disease, in accordance to the reports of other researchers [2–4, 7, 8]. No malignant lesions were diagnosed during our study, as depicted by literature data [1, 4, 14, 15], but this does not exclude the possibility of their occurrence. Extending the studied group, to comprise a larger number of patients, including other geographic regions, might depict digestive neoplasms as well.

Our study remarked the possible co-existence of several gastrointestinal disorders at the same time, as described in literature [4, 9]. We noted the case of one severely immunocompromised patient, with CD4+ T-cells level 28/μL, co-infected with HBV, who suffered simultaneously from *Candida* esophagitis, as well as intestinal cryptosporidiosis and *Shigella dysenteriae* infection. This concurs to the literature observation that, in an HIV-infected patient, even after diagnosing one cause of digestive disease, the physician must not stop searching for other possible etiologies [4, 9].

Literature data report a change in gastrointestinal pathology of HIV-infected patients following the initiation of antiretroviral therapy [3, 7]. If, during the first years after the discovery of HIV, severely immunosuppressed patients were suffering from digestive opportunistic infections or malignities [9], the extensive use of HAART lead to a decline in gastrointestinal AIDS-defining illnesses, making room for non-HIV-related disorders [7]. Some, like GERD and peptic ulcer [7], are similar to those encountered in the general HIV-negative population; others are the consequence of medication adverse events [6].

Although we did not intend to perform a comparison regarding gastrointestinal pathology before and during the HAART era, like other researchers [3, 7], as our study was limited in time to a more recent interval (2006–2013), when antiretroviral medication was universally available in our country, we evaluated the range of digestive tract disorders among HIV-infected patients undergoing HAART comparing to those not receiving it. This second group was composed of non-adherent or newly diagnosed patients, as well as cases of therapeutic failure, when resistance of the HIV strain to antiretroviral substances was considered. Patients under HAART developed significantly less opportunistic infections than those not receiving antiretroviral medication (p=0.0375, OR=0.2030, 95% CI 0.0423–0.9741). This concurs to literature data who report AIDS-defining illnesses during HAART era [10, 11] mostly in HAART-naïve patients or late presenters [2].

The most frequent AIDS-defining condition diagnosed in our group was *Candida* esophagitis – nine (23.68%) patients. We found that patients suffering from this opportunistic infection had significantly lower CD4+ T-cell counts than those diagnosed with non-HIV-associated conditions (p=0.0043). This concurs to literature data stating that CD4+ T-lymphocytes levels less than 200 cells/μL predict the development of an HIV-associated disease [8].

While 10 out of our 17 patients with CD4+ T-cells count less than 200 cells/μL developed digestive opportunistic infections: *Candida* esophagitis or intestinal cryptosporidiosis, 14 out of the 21 HIV-infected patients with higher CD4+ T-cells level presented non-HIV-associated conditions: GERD, antral erythematous or erosive gastritis, enterogastric reflux gastritis, hiatal hernia, duodenitis or duodenal ulcer, hemorrhoidal disease, but other two cases of focal active colitis and one case of HIV enteropathy were reported as well.

Although eight (21.05%) patients had been diagnosed with pulmonary or extrapulmonary tuberculosis (TB), none of the subjects from our study had confirmed intestinal TB. This, however, does not exclude the possibility of developing digestive tract infection with *M. tuberculosis* or *M. avium* complex, as reported by other authors [2, 10].

Non-HIV-associated diseases are not to be ignored, though. An important number of HIV-infected patients presented with endoscopic and histopathological features of GERD, Barrett esophagus, erythematous or erosive gastritis, duodenal ulcer or duodenitis. Gastrointestinal symptoms caused by these conditions – abdominal pain, nausea and vomiting –, may decrease the patients' adherence to HAART and thus lead in time to the impairment of his immunologic status. On the other hand, medication adverse effects may cause these symptoms [6]. Twenty-two (57.89%) patients were under HAART, but a significant number of other types of medication were prescribed to HIV-infected patients as well, including anti-TB treatment in eight (21.05%) cases and steroidal or NSAIDs in 16 (42.11%) cases.

Diarrhea, considered the most frequent digestive complaint in HIV-infected patients [2], was encountered in seven (18.42%) patients in our study. Its etiology varied from OI (intestinal cryptosporidiosis) to bacterial colitis, reflected upon pathologic examination by focal active colitis, and HIV enteropathy. The latter, an effect of HIV itself upon the mucosa of the digestive tract, did not display endoscopic changes and was diagnosed based on pathological examination of colonic biopsies, revealing villous atrophy, crypt hyperplasia, apoptotic bodies inside

epithelial cells. It is considered one of the main causes of malabsorption, chronic diarrhea and weight loss in HIV-infected patients [1, 2, 16].

Wasting syndrome, an AIDS-defining illness in the CDC classification of HIV infection [5], expressed by a weight loss of more than 10% in the absence of any underlying infections of malignity, associated to fever, diarrhea or fatigue [1], affected 16 (42.11%) subjects.

Histopathological examination of biopsies supported the endoscopic diagnosis. Endoscopic diagnosis of esophageal candidiasis, based on the presence of white mycotic deposits located on the hyperemic esophageal mucosa, with areas of ulceration, was confirmed by histopathological examination, depicting acanthosis and hyperplasia of the epithelial cristae, along with inflammatory cells, while Alcian blue/PAS stain revealed the presence of *Candida albicans* hyphae. GERD endoscopic diagnosis was supported by histopathological findings of columnar epithelium with goblet cells suggesting the development of Barrett's esophagus. Several cases of erythematous antral gastritis on endoscopy, with minor histopathological changes, including foveolar hyperplasia, chorion edema and vascular congestion, as well as reduced inflammatory infiltrate, were interpreted as reactive gastropathy. Chronic duodenitis was depicted, with shortened and thickened villi and abundant inflammatory infiltrate in the chorion.

Discordant results between endoscopy and histopathological examination were reported as well. Focal active colitis on histopathological examination, with polymorphonuclear infiltrate and microscopic abscesses in the colonic walls, pointed towards infectious etiology in two patients complaining of diarrhea, even when stool cultures were negative and endoscopy suggested an inflammatory bowel disease, with favorable outcome under antibiotic therapy.

The observation that HIV enteropathy evolves with negative endoscopies, but significant changes upon histopathological examination, reported in literature [2, 16] and confirmed by our study, underlines the importance of pathological examination of biopsies in all cases, even when endoscopy did not reveal any alterations. However, there is the issue of patients' lack of collaboration during the procedure or the existence of contraindications for biopsy sampling, mainly due to coagulation disorders (thrombocytopenia, deficit of coagulation factors due to liver failure). HIV-infected patients, even experiencing gastrointestinal symptoms, may prove reluctant to invasive maneuvers, including biopsies and sometimes even endoscopic examination, due to the multitude of other invasive procedures required by extra-digestive diseases: lumbar punctures, lymph node biopsies, bone marrow examination, thoracentesis or paracentesis. Although bacteriological/mycological/parasitological stool examination is sufficient for etiologic diagnosis in about half of HIV-infected patients with gastrointestinal complaints [1, 12], other cases require endoscopy and pathological examination for establishing the diagnosis [4, 13].

One-third – 13 (34.21%) patients – died during the study, at various distances from endoscopic examination: one month to two years. All patients were in AIDS stage. Six (46.15%) of them had been previously diagnosed with a fungal or parasitical digestive OI. However, the main cause of death was not the digestive tract disorder, even in case of a gastrointestinal OI, but pulmonary and extrapulmonary TB, including multi-drug-resistant *M. tuberculosis* or *M. avium* complex infection, and central nervous system conditions – mixed, cryptococcal and tuberculous meningitis. Although the gastrointestinal illness did not represent the direct cause of death in these patients, it may predict the risk of development of another AIDS-defining lethal condition in the near future.

Conclusions

HIV-infected patients develop a variety of digestive tract disorders, ranging from opportunistic infections to non-HIV associated conditions, some similar to those encountered in the HIV-negative population. Patients suffering from digestive OI have lower levels of CD4+ T-lymphocytes than those diagnosed with other gastrointestinal conditions (p=0.0043). The most frequent digestive AIDS-defining illness in our study was esophageal candidiasis, affecting 23.68% subjects. We found a statistically significant negative association between highly active antiretroviral therapy and the presence of digestive tract OI (p=0.0375, OR=0.2030, 95% CI 0.0423–0.9741). Patients undergoing HAART were more likely to experience non-HIV-associated conditions, such as GERD, acute/chronic gastritis and duodenal ulcer.

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