

Cytomegalovirus Superinfection in Chronic Inflammatory Bowel Diseases: Prevalence and Therapeutic Implications

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Abstract

Original Research Article

Introduction: The screening of CMV infection during inflammatory bowel disease (IBD) flare-ups is necessary to support the diagnosis and to carry out the therapeutic management. The objective of our work is to define the prevalence of CMV infection during IBD and to optimize the therapeutic attitude. **Materials and Methods:** Our work is a retrospective study carried out on the whole of 5 patients of the service of gastroenterology of the HMIMV-Rabat. The diagnosis is based on the detection of anti CMV immunoglobulin, CMV pp65 antigen, viral DNA by PCR on a sample of blood or colonic mucosa and by histology and immunohistochemistry techniques during IBD exacerbations. **Results:** The mean age of the patients was 33,6. The sex ratio is 2F/3H. The clinical manifestations were predominantly abdominal pain, bloody stool and a rectal syndrome. The mean hemoglobin, CRP and albumin levels were 9.8g/dl; 56.2mg/l and 21.2 g/l respectively. Two of the five patients had severe lesions on endoscopy. The prevalence of CMV superinfection during IBD is calculated to be 7.7%. Ganciclovir was administered in 3 patients and two received valganciclovir. Four patients were treated with combination therapy (Infliximab+Azathioprine), and one patient received Mesalazine. **Conclusion:** CMV superinfection during IBD is not rare, and requires specific antiviral treatment associated with the treatment of the inflammatory disease flare-up.

Keywords: Cytomegalovirus-severe acute colitis-IBD.

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INTRODUCTION

Cytomegalovirus (CMV) is a member of the herpesvirus family and is a common infection in humans, affecting 40–100% of adults [1]. Clinically significant CMV gastrointestinal disease usually occurs in immunocompromised individuals; among others, patients who have undergone a bone marrow or organ transplant, those on corticosteroid therapy, as well as cancer patients undergoing chemotherapy. In inflammatory bowel disease (IBD), the frequency of CMV infection is rare, varying between 0.53%-3.4percent [2]. This frequency rises to 11 to 36% during severe attacks [3]. It is most often a viral reactivation, rather than a primary infection [4]. Chronic inflammation is considered to be a factor favoring infection, and immunosuppressive treatments can increase this risk [5].

Our work aims to: Report the experience of the gastroenterology department of the HMIMV in Rabat, assess the prevalence of cytomegalovirus superinfection during IBD exacerbations and discuss the therapeutic options to be offered in the face of CMV superinfection during IBD flare-ups.

MATERIALS AND METHODS

I. Patients:

Our work constitutes a descriptive retrospective study carried out within the department of gastroenterology I at the Military Hospital of Instruction Mohammed V (HMIMV) -Rabat. The study is carried out on all patients hospitalized in the department for an attack of chronic inflammatory bowel disease IBD presenting with cytomegalovirus superinfection, over a period of two years. From January 2019 to January 2021, five patients infected with CMV were hospitalized out of a set of sixty-five patients. In our series, the diagnosis is based on the demonstration during an exacerbation of IBD of:

- IgM anti-CMV antibodies on serology, and/or
- Viral genome by PCR on blood sample and endoscopic biopsy and/or
- Presence of viral inclusion on hematoxylin and eosin (H&E) staining of a fragment of colonic tissue.

The data collected is:

1. Epidemiological data: age, sex, personal history, smoking, family history of IBD.

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2. Clinic: Reason for admission, general signs, digestive signs, extra-digestive signs
3. Biology: Hemoglobin level, CRP, albuminemia, Leucocyte
4. Morphology: Endoscopy, Imaging
5. Severity scores: TRUELOVE and WITTS, LICHTIGER
6. Treatment: Treatment of IBD outbreak, treatment of CMV infection

II. Statistical analysis: Statistical analysis was studied using SPSS20 software.

RESULTS

I. Epidemiological results:

1. Age: Our study is carried out on 5 patients of different ages ranging from 26 to 58 years old with an average age calculated at 33.6 years [± 12.05]

2. Gender: Women represent 40% of the patients who had superinfection with CMV in our series. Men account for 60% of all affected cases. •Sex ratio F/M: 2/3.

3. Personal history of inflammatory bowel disease: Among the superinfected patients, three are known carriers of IBD, while two patients present an inaugural IBD.

4. Family history of IBD: None of the patients has a family history of IBD.

5. Tobacco: Only one patient is a smoker.

II. The clinical examination:

1. Admission:

Table 1: Means of clinical parameters

Clinical signs	IBD with CMV+
Stools/day (standard deviation)	13,4 (2,33)
rectal syndrome	40%
Average heart rate (standard deviation)	90 bpm (1,8)
Abdominal pain	100%
deterioration of general condition	60%
T°	37,4

2. Biological results

Certain biological parameters make it possible to assess the severity of the disease; in this regard we use the hemoglobin level, the plasma concentration of CRP and albumin.

1. Hemoglobin The average hemoglobin level is 9.84 g/dl [± 1.45]

2. C-Reactive Protein: The average CRP value is 56.2 mg/L [± 12.13]

3. Albumin: Mean serum albumin is 21.6 g/L [± 4.4]

4. IBD severity scores:

Table 2: Severity scores.

THE SCORE	THE AVERAGE VALUE OR PERCENTAGE
TRUELOVE et WITTS	80% severe 20% moderate
LICHTIGER	13,25

III. Morphology:

1. Endoscopy:

It is performed in an emergency except for contraindications; it allows to assess the presence or absence of severe lesions and to perform biopsies.

Contraindications of colonoscopy:

Colonoscopy is contraindicated in the event of perforation or peritoneal syndrome, these complications being indications for immediate colectomy. The presence of colonic dilation should encourage caution by insufflating at least and favoring CO₂ (if available) during an examination most often limited to the rectosigmoid. The presence of colectasis will be a contraindication to an endoscopic procedure.

Severe endoscopic lesions:

- Digging ulceration.
- Pit ulceration.
- Mucous detachment.
- Mucosal abrasion.
- 40% of patients had severe lesions.

2. Abdominal CT:

Often performed before endoscopy and allows to highlight radiological abnormalities and their topography: The signs to look for are: colonic abscess, colectasis and colonic perforation. The presence of a single element justifies emergency surgery. None of the patients had any signs of complications immediately on CT.

Topography of lesions:

- 40% pancolitis
- 40% left colitis
- 20% colitis occupying the left colon and the transverse colon.

Screening for cytomegalovirus infection is imperative in the face of IBD flare-ups, it is in this context that our patients were diagnosed. It is based on the search for immunoglobulins of type M and G as well as the detection of viral DNA on blood or colon cells by a PCR chain polymerization reaction.

The table below details the means of diagnosis in our patients:

IV. Diagnosis of cytomegalovirus infection:

Table 3: Diagnostic elements in our patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
IgM		+	+		doubt
IgG	+			+	
PCR in blood		+		+	
PCR on biopsy	+	+	+	+	+
H and E coloring	-	-	-	-	-

- The diagnosis of hemorrhagic recto colitis was retained in the five patients in our series.
- In all our patients, the diagnosis of a CMV infection was retained by the positive viral PCR in the colon biopsies.

V. Prevalence of CMV superinfection:

The prevalence is the objective of our study, it is defined as all cases with a disease in a period of time, taking into consideration both new cases and old cases. In our context, we are trying to calculate all the patients who have had a superinfection with cytomegalovirus during an IBD flare-up.

The result is as follows: five patients superinfected with CMV among sixty-five who had an exacerbation of IBD over a period of two years, thus generating a prevalence of 7.7%.

VI. Treatment:

1. Treatment of IBD flare-up

The management of IBD flare-ups in our patients was initiated by the introduction of corticosteroid therapy in four patients, at a rate of 60mg of methylprednisolone intravenously per day. The evaluation after seven days of treatment made it possible to conclude that corticosteroid therapy had failed justifying the use of combo therapy associating infliximab (Remicade) and azathioprine (Imurel).

One in five patients had a moderate flare-up of ulcerative colitis requiring the administration of mesalazine (Pentasa) orally and an intra-rectal enema.

2. Antiviral treatment

All patients infected with CMV received an antiviral treatment, of which three (60%) were treated with ganciclovir (Cymevane) and two most recently diagnosed were treated with valganciclovir (Rovalcyte) according to the following protocol:

Table 5: The antiviral treatment received by our patients:

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
The treatment instituted	Valganciclovir (rovalcyte®)	Ganciclovir (cymevan®)	Ganciclovir (cymevan®)	Ganciclovir (cymevan®)	Valganciclovir (rovalcyte®)
The way	Oral	Intravenous	Intravenous	Intravenous	Oral
The dose	450mg*2/12H	5mg/kg/12H	5mg/kg/12H	5mg/kg/12H	450mg*2/12H
The duration of treatment	21 days	21 days	21 days	21 days	21days

VII. Evolution

-All patients in our study responded to antiviral treatment. They improved clinically and biologically.

Table 6: Evolution of clinical and biological parameters after seven days of antiviral treatment:

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Stools/day	2	1	2	1	Saddle one day/2
Abdominal pain	Disappeared	Disappeared	Disappeared	Disappeared	Disappeared
CRP	<5	<5	<5	<5	<5

- No control PCR (CMV) was performed on colonic biopsy in our patients

DISCUSSION

Multiple studies have been performed to identify factors that may increase the likelihood of acquiring CMV infection in patients with IBD.

Between 2006 and 2011 a study by Yi and al. found that elevated CMV was mainly associated with severity of disease activity ($P = 0.048$), use of ASA/SASP therapy and corticosteroids ($P=0.041$ and $P=0.035$ respectively). While other factors, such as age, sex, smoking, alcohol consumption, type of diet, fever, anemia, albumin level, disease location, treatment with immunosuppressive agents did not show a significant association ($P > 0.05$) [6].

H.Lee and al. in their study found that CMV superinfection occurs as part of an IBD flare most often in patients who have been treated with high doses of corticosteroid therapy, and in those with ulcerated lesions on endoscopy with a high Mayo score [7].

Similar results were obtained in the study by Hirayama and al. which revealed that a total dose of corticosteroids > 400 mg for 4 weeks, an extensive colitis and deep ulceration are associated with an increased risk of CMV infection. in patients with moderate to severe UC [8].

Factors that have been associated with an increased risk of CMV reactivation in IBD include:

Female gender, pancolitis, advanced age greater than 30, immunosuppressive treatment (steroids and azathioprine) (OR 6.7), disease duration less than 60 months (OR 7.7) and a number blood leukocytes less than $11/nL$ (OR 6.7) [68,69,70]. Although chronic infliximab use was not associated with an increased risk of CMV infection in two studies, a strong association was observed in another third [9,10,11].

In our series, the risk factors objectified in our patients are: UC, corticosteroid resistance, pancolitis and endoscopic ulcerations.

CMV colitis is diagnosed by histological method (hematoxylin and eosin staining; immunohistochemistry), PCR on biopsy or by viral culture.

H&E staining typically reveals cytomegalic cells two to four times larger than normal cells, containing off-centered basophilic intranuclear inclusions surrounded by a clear halo, giving it an "owl-eye" appearance. The cells show a thickened nuclear membrane and smaller granular intracytoplasmic inclusions. Colonic biopsies should be taken from the inflamed mucosa near or inside the ulcer. This method has a very high specificity (92%-100%), but its main problem is a low sensitivity (10%-87%), which means that the diagnosis requires many samples and a trained pathologist [12]. Anecdotally, cytomegalic cells have

been described in colon biopsies from normal mucosa in healthy individuals [13].

Antiviral treatment is not necessarily indicated for all patients with IBD and CMV infections. Maconi and al. found that antiviral therapy did not greatly influence the long-term outcomes of patients with IBD and active CMV colitis [14]. However, in UC patients who were notably steroid-dependent or refractory, those who received antiviral treatment experienced a significantly higher rate of clinical remission (77.8%) at 12 months compared to those who did not. did not receive this treatment (19.4%, $p = 0.038$) [14]. A recent meta-analysis showed that antiviral agents did not reduce the risk of colectomy in unselected UC patients with CMV [15]. However, antiviral therapy significantly reduced this risk in CMV-infected patients refractory to corticosteroids. Kim and al. studied 31 patients with UC and CMV infections, and found that 17 of them, whose symptoms improved on corticosteroids, did not need antiviral treatment [16]. However, the other 14 patients (who did not respond to corticosteroid therapy) required ganciclovir [16]. Thus, antiviral therapy is only necessary for a small group of patients with IBD.

It is now well established that corticosteroids and immunomodulators are associated with an increased risk of CMV reactivation [17,18]. In a prospective study of 61 patients with UC, treatment with azathioprine in addition to steroids was found to be a significant risk factor for CMV infection, defined by the presence of positive IgM antibodies or detection of CMV DNA by PCR on a colon biopsy or positive histological results of a colon biopsy stained with H and E [69].

A recent meta-analysis by Shukla and al [9] showed that exposure to corticosteroids and thiopurines was associated with an increased risk of CMV reactivation. However, this risk could not be demonstrated when using tissue CMV PCR for diagnosis.

Treatment with an anti-TNF alpha had no negative effect on patients with CMV reactivation [19, 20]. Although no studies have specifically examined the effect of anti-TNF alpha on viral replication in patients with UC and CMV, these agents could theoretically lead to a reduction in macrophage differentiation and CMV reactivation [21].

CONCLUSION

CMV superinfection is increasingly found during flare-ups of chronic inflammatory bowel disease; UC, extension of the disease and resistance to corticosteroid therapy are the most frequently identified risk factors. The place of CMV in exacerbations is still a subject of debate.

Screening for CMV is necessary for all patients with moderate to severe IBD. CMV can be diagnosed by

histological IHC staining and tissue PCR; blood tests such as Ig antigen and CMV PCR can help in early diagnosis and predict clinical course. The prescription of antiviral therapy can be based on clinical status and viral load in the colon.

Many analyses, meta-analyses and algorithms have been proposed for the management of CMV superinfection in patients with IBD. Despite this, there are still many unanswered questions related to the optimal diagnosis of SCMV, the criteria to use, the course of action to take concerning corticosteroids, immunomodulators, anti-TNF agents.

Current guidance considers anti-TNF therapy as an adjunctive therapy that may be considered to treat SCMV-associated flares in patients with IBD, in combination with antiviral therapy. However, a large-scale study is needed to explore the utility of immunomodulators as a treatment for CMV complicating IBD.

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