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Is it justified to order an upfront cytomegalovirus immunohistochemical stain in patients with severe inflammatory bowel disease and ulceration?

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ABSTRACT

Background: Cytomegalovirus (CMV) infection is common amongst both immunocompetent and immunocompromised patients. Patients with inflammatory bowel disease (IBD) are more prone to suffer from CMV complications. In this study, we investigated the utility of immunohistochemistry to diagnose CMV infection in patients with severe IBD.

Methods: We searched our pathology data system to identify patients with IBD from January 1, 2017 to December 31, 2021. We identified 5782 IBD cases, out of which 784 cases had severe activity with ulceration. CMV immunohistochemical stain (IHC) was performed on all 784 cases. Hematoxylin and eosin (H&E) staining slides were reviewed to evaluate the presence of characteristic nuclear or cytoplasmic CMV inclusions. H&E and IHC results were categorized as "single" if 1 cell stained positive or had characteristic inclusions, "rare" if 2-5 cells stained positive or had characteristic inclusions and "many" if more than 5 cells stained or had characteristic inclusions. Clinical outcomes, treatment and serum CMV viral loads were examined.

Results: A total of 29 cases out of 784 cases (3.7%) were positive for CMV by IHC. Seven cases (0.9%) showed many positive cells, 14 (1.8%) had rare positive cells and 8 cases (1%) showed single positive cells on IHC. The most frequently involved specimen type was the left colon. Twelve out of 29 cases (41%) didn't show characteristic cytoplasmic or nuclear inclusions on H&E stains prior to IHC. Out of these 12 cases, CMV IHC showed rare cells in 7 cases (58%) and single cells in 5 cases (42%). None of these cases show many positive cells on IHC. CMV viral load PCR was tested in 10 out of 29 cases (34%) and was positive in 80% of tested patients (8 out of 10). The majority of positive cases by PCR had many CMV inclusions on IHC (5 out of 8, 63%). Only 3 out of 12 patients with no H&E inclusions were tested with CMV PCR with 2 cases being positive (2 out of 12, 17%). These 2 cases were treated with antiviral treatment. Overall, CMV IHC helped to detect CMV positivity in only 12 out of 784 cases (1.5%) that were otherwise not apparent on H&E.

Conclusions: These results suggest that CMV infection is rare in IBD patients with severe activity and ulceration and H&E should be used as a first line to detect viral inclusions in such patients. CMV IHC could only help to identify the CMV infection in a minority of cases with no characteristic inclusions on H&E stain.

1. Background

IBD is a debilitating disorder characterized by chronic relapsing inflammation of the gastrointestinal tract and can cause serious implications for patients. IBD involves two main entities, Crohn's disease (CD) and ulcerative colitis (UC). Based on a study done by Global Burden of Diseases IBD Collaborators reviewing the data of 195 countries between 1990 and 2017, the prevalence of IBD is increasing rapidly in many regions [1]. Although the mechanisms are not well defined, this rapid change can be attributed to environmental factors, such as smoking, diet, pollution, antibiotics, and psychosocial stressors. IBD has a major impact on all aspects of patients' lives and poses a heavy burden on healthcare systems. Pathogenesis of IBD and accompanying conditions such as viral infections have been widely studied [2,3]. Some evidence indicates that human CMV infection can be associated with the onset of IBD especially in refractory to treatment patients [4,5]. Furthermore, the high prevalence of CMV has been reported in UC (up to 81%) and CD patients (up to 66%) [6].

CMV is a herpesvirus and causes a broad range of clinical syndromes. In the immunocompetent host, primary CMV infection is usually

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asymptomatic. Clinical manifestations in the immunocompromised patient can range from a short febrile illness to multiple organ system involvement. CMV establishes latency in bone marrow hematopoietic progenitor cells [7], endothelial cells and macrophages [8]. Replication of CMV in these cells plays an important role in enabling the virus to maintain a life-long infection.

Patients with IBD are more prone to suffer from CMV complications, sometimes CMV can cause significant morbidity and even mortality in this patient population. The association between CMV and IBD is not new. The earliest CMV case report in a UC patient we could find was published in 1961 by the American Journal of Medicine [9] and rare case reports were published during the 1970s and 1980s [10,11]. The effort to understand the association between IBD and CMV continued throughout 1990 and 2000s [12,13]. However, the question about the role of CMV in these patients remains the same. It is not known whether the virus exacerbates the disease or simply appears as a bystander of severe disease [14] or could be a consequence or cause of the disease severity and steroid refractoriness [13].

Different publications also reported a wide range of CMV prevalence or reactivation ranging from 4.5% to 30% in moderate to severely active UC patients [12,15–17]. IBD patients with CMV infections seem to have a worse outcome, however, remission rates with antiviral therapy are reported as high as 86% [12]. Only rare studies have investigated the prevalence of CMV in colonic biopsies and showed a prevalence of 10% in patients with UC [18]. Yet no official guideline exists on the use of upfront or subsequent CMV IHC in such patients. This study aims to evaluate the use of upfront CMV IHC in detecting the CMV virus in both UC and CD patients.

2. Material and method

2.1. Study design and patient selection

We searched our pathology data system to identify patients with IBD from January 1, 2017 to December 31, 2021. We identified 5782 IBD cases, out of which 784 cases had severe activity with ulceration. CMV immunohistochemical stain (IHC) was performed on all 784 cases. In all cases, pathology reports and H&E slides were reviewed. Clinical information such as patient's age, gender, relative comorbidities, CMV viral load (Roche COBASAMpliprep TaqMan CMV test), and treatments were recorded.

2.2. Pathology studies

H&E slides were reviewed to evaluate the presence of characteristic nuclear or cytoplasmic CMV inclusions. H&E-stained slides were evaluated and categorized as “single” if only one cell had characteristic inclusions, “rare” if 2-5 cells had characteristic inclusions and “many” if more than 5 cells had characteristic inclusions. IHC studies were performed on 4-μm sections obtained from the paraffin blocks of the selected biopsy samples using monoclonal antibodies directed against CMV (Cell Marque, 213m-25, 1:100 dilution). The IHC slides were read independently by 2 pathologists. The slides were scored similarly to H&E slides and categorized as negative or positive with further categorization as “single” positive cells if one cell stained for CMV IHC, “rare” if 2-5 cells were stained, or “many” if more than 5 cells show positivity by CMV IHC. Moreover, CMV IHC positivity among cases with no apparent inclusion on H&E was investigated. Available results of serum CMV viral loads performed within 3 weeks of the procedures were recorded in IHC positive patients. Clinical outcomes and treatment regimens were documented.

2.3. Statistics

Descriptive statistics are reported as mean ± standard deviation. Statistical Analysis including the Students' t-test for continuous variables and Fisher's exact tests for categorical variables were performed. The 2-sided level of confidence was set at P-value<0.05. Multivariate analysis was not possible due to the insufficient number of patients with CMV infection.

3. Results

3.1. Patient population

During the 5-year period from 2017 to 2022, we identified 5782 IBD cases in our institution. Out of which, 784 cases demonstrated severe activity and ulceration. CMV IHC was performed on all the severe cases. Total of 29 cases out of 784 cases (3.7%) were positive for CMV by IHC. Twenty-one patients out of 29 had UC, 7 had CD and one had indeterminant colitis. The age of patients with CMV IHC positivity ranged from 22 to 94 years old (mean: 51.9 ± 16.7). Fifteen patients were female, 11 were male (female to male ratio of 1.4 to 1). Three patients had more than one specimen (2 each) during our study period. One patient (a 40-year-old female) died from fallopian tube carcinoma. The most frequently involved specimen type was the left colon (18/29, 62%). Other involved areas were both the right and left colon (3/29, 10%), ileum (2/29, 7%), right colon (1/29, 3%), and transverse colon (1/29, 3%). For the remaining 4 cases (4/29, 14%), the location of the colonic biopsy was not specified.

3.2. Histological correlation

Out of 29 CMV positive cases, seven cases (24%) showed many positive cells, 14 (28%) had rare positive cells and 8 cases (27%) showed a single positive cell on IHC. We evaluated the H&E slides of all 29 IHC positive cases to see if we could appreciate the CMV viral inclusions on H&E alone. Characteristic CMV viral inclusions were appreciated in 17 out of 29 cases (59%). On the other hand, 12 out of 29 cases (41%) did not demonstrate any characteristic viral inclusions on H&E stains. In cases where no CMV viral inclusions were appreciated on H&E, CMV IHC showed rare cells in 7 cases (58%) and single cells in 5 cases (42%). None of these cases showed many positive cells on IHC. All seven cases that had many positive cells by IHC revealed characteristic CMV viral cytopathic effect on H&E (Fig. 1). Characteristic CMV viral inclusions were seen on H&E alone in 8 out of 14 cases (57%) in the rare group. On the other hand, CMV viral inclusions were visible on H&E in only 2 out 8 cases (25%) in the single positive group by IHC (Table 1).

CMV IHC helped to detect CMV positivity in 12 out of 784 cases (1.5%) that were otherwise not apparent on H&E.

3.3. Clinical data of the patients with CMV infection

CMV viral load was only checked in 34% of the CMV IHC positive cases by polymerase chain reaction (PCR). Not surprisingly 80% of the tested ones were positive. For each category of single, rare, and many by IHC, CMV PCR results have been analyzed separately. The majority of PCR positive cases (5 out of 8, 62%) had many viral inclusions. CMV PCR results in the single group by IHC were available only in one patient (12.5%) and it was negative. In the rare group, CMV PCR was available in 3 cases (21%) and they were positive. In the many group by IHC, 1 case (14%) was not tested by CMV PCR, and 5 out of 6 (83%) came back positive by CMV PCR. Only 3 out of 12 patients with no H&E inclusions were tested with CMV PCR with 2 cases being positive. These 2 cases were treated with antiviral treatment.

CMV PCR numerical values have been grouped per IHC results (Table 2). Mean PCR value of the cases with rare CMV inclusions is 429 ± 353; and in the many group is 15,319 ± 22,314. We furthermore reviewed subsequent pathology specimens for the 19 patients who did not have CMV PCR testing at the time of diagnosis. Of these 19 cases, 13 patients (68%) had follow-up biopsies within a few months, none of which demonstrated CMV viral cytopathic changes. One additional

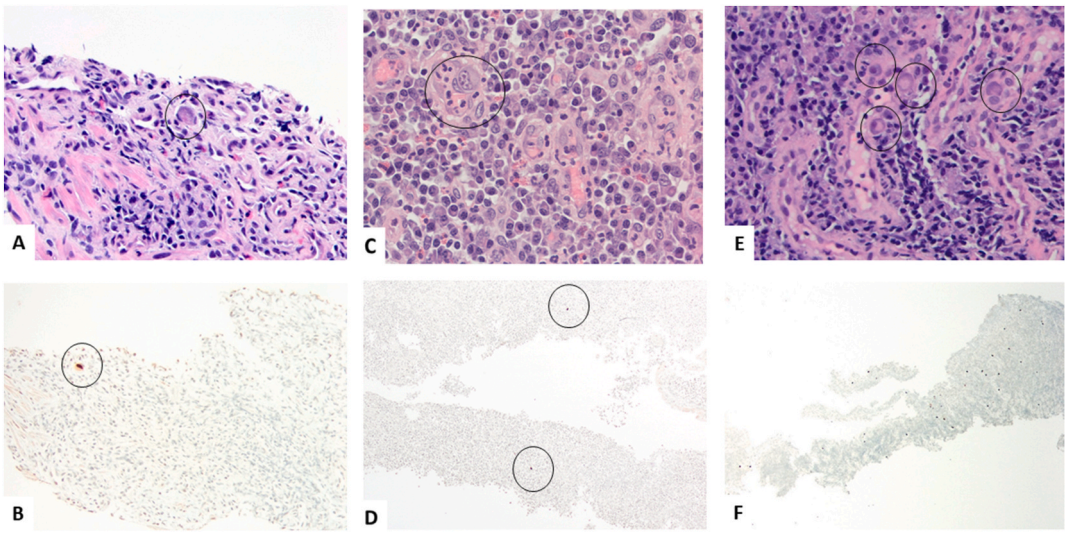

Fig. 1. Representative histopathologic and immunohistochemical staining features. A. High power view of the single large ovoid CMV intranuclear inclusion in lamina propria (H&E), highlighted by a circle B. Single strong nuclear staining by CMV immunohistochemical stain, highlighted by a circle. C. Two large pleomorphic nuclei with basophilic intranuclear inclusions (H&E), highlighted by a circle. D. Two CMV infected cells showing immunoreactivity with CMV immunohistochemical stain, highlighted by circles. E. Cytomegalic endothelial cells with prominent basophilic nuclear inclusions by H&E, highlighted by circles. F. Low-power view of many CMV infected cells showing immunoreactivity with CMV immunohistochemical stain.

Table 1
CMV Immunohistochemistry; histologic and clinicopathological correlation.

CMV IHC	# Cases	Presence of CMV viral inclusions on H&E	CMV PCR	Antiviral Treatment
Single	8	2	1 negative (7 not tested)	12.5% treated
Rare	14	8	3 positive (11 not tested)	50% treated
Many	7	7	5 positive, 1 negative (1 not tested)	86% treated

Table 2
Correlation between CMV IHC results and PCR values.

CMV IHC	CMV PCR (IU/mL)
Single	Negative
Rare	41
Rare	733
Rare	513
Many	57,600
Many	14,400
Many	Negative
Many	312
Many	19,300
Many	306

patient underwent colectomy, which also showed no evidence of CMV infection. Four patients had no follow-up specimens available. The remaining one case had a follow-up biopsy two years later, which was negative for CMV infection.

Antiviral treatment data was reviewed in each category. In the single group by IHC, only 1 patient (1/8, 12.5%) was treated with an antiviral regimen, 6 patients (75%) didn't get any antiviral treatment, and 1 patient was lost to follow-up. In the rare group; 7 patients (7/14, 50%) got antiviral treatment, 6 patients (42.8%) didn't get any treatment, and 1 patient was lost follow-up. Out of the treated ones, 1 patient developed cytopenia due to valgancyclovir. In the many group, 6 patients (6/7, 86%) got treatment, and 1 patient (14%) didn't get any treatment. No patient in this group developed any side effects.

The requirement of colectomy within 6 months was evaluated in between the groups. In the single group, only 1 patient (12.5%) had subtotal colectomy due to not responding to medical treatment. In the rare group, 4 patients (28.6%) had colectomy. In the many group, 2 patients (28.6%) required colectomy in 6 months (Table 3).

Additional clinical data was reviewed including hospitalization to control IBD symptoms and prior steroid treatment. In the single group, 3 cases (37.5%) required hospitalization, including one with more than 7 days of hospitalization (12 days). The mean value of the length of hospital stay was 6 ± 5.2.3 (37.5%) cases were taking steroids prior to the specimen collection. In the rare group, 3 cases (21.4%) required hospitalization with 2 of them requiring 16 and 7 days. The mean value of the length of hospital stay was 8.3 ± 7.09.6 cases (42.8%) were taking steroids prior.

In the many group, all cases required hospitalization (100%), and vast majority of them (85.7%) stayed longer than 7 days. The mean value of the length of hospital stay was 16.3 ± 9.32.6 cases (85.7%) were taking steroids prior to the specimen collection (Table 4).

4. Discussion

CMV infection prevalence and its role in active IBD have been controversial. Several studies reported that patients with fulminant IBD, patients treated with certain immunosuppressive agents, and older patients refractory to medical therapy may be particularly at risk for CMV infection [19–21]. On the other hand, rare studies also challenge the pathogenicity of CMV by showing a lack of correlation between CMV and the clinical severity of IBD [22]. There is also a possibility that CMV can be an innocent bystander in the colonic mucosa of patients with active IBD. Reviewing 5-year data of our academic center demonstrated that only 3.7% of the IBD patients with severe activity were positive for CMV with immunohistochemistry. Hommes et. all published a systematic review aiming to understand the pathogenicity of CMV in IBD

Table 3
Requirement of surgery within 6 months of each subgroup.

CMV IHC	Requirement of surgery within 6 months
Single	1 (12.5%)
Rare	4 (28.6%)
Many	2 (28.6%)

Table 4
Clinical outcomes of patients for each subgroup.

CMV IHC	# Cases	# Cases required hospitalization	#Cases required ≥7 days of hospitalization	Length of hospital stay (days)	Mean value of the length of hospital stay	# Cases taking steroids prior
Single	8	3 (37.5%)	1 (12.5%)	12, 3, 3	6 ± 5.2	3 (37.5%)
Rare	14	3 (21.4%)	2 (14.3%)	16, 2, 7	8.3 ± 7.09	6 (42.8%)
Many	7	7 (100%)	6 (85.7%)	13, 28, 28, 18, 2, 12, 13	16.3 ± 9.32	6 (85.7%)

patients in 2004 [23]. The prevalence of CMV colitis in resected IBD specimens in their retrospective review ranged from 0 to 17.9% [23]. Other studies showed higher percentages of CMV positivity up to 36% in steroid-resistant IBD patients in histological specimens and in the buffy coat of their blood samples [24].

To this day, pathologists still wonder if they need to do CMV IHC on the biopsy specimen from patients with active IBD and ulceration. This study aims to answer that question by evaluating the correlation between the presence of characteristic CMV viral cytopathic effect (VCPE) on H&E and IHC results and determining the possibility of detecting CMV infection without using IHC. More than half (59%) of the IHC positive cases demonstrated characteristic VCPE on H&E, and more reassuringly, none of the cases with nonvisible viral cytopathic effects on H&Es demonstrated 'many' CMV cells on IHC. The ratio of CMV viral cytopathic effect presence on H&E is nicely correlated with the amount of CMV positive cells on IHC (25% in the single group, 57% in the rare group, and 100% in the many group).

CMV PCR was not widely ordered by the clinician in our cohort, either due to it not being clinically indicated or histological proof was thought to be satisfactory enough. Among our groups, many by IHC group is the most tested group by PCR, and the majority of PCR results came back positive (83%). Moreover, CMV PCR numerical values tended to be higher in many group compared to the other groups. Thus, the number of CMV positive cells on IHC correlates with numerical CMV PCR values.

Our data shows that a higher percentage of cases with more CMV inclusions received antiviral treatment and, they had a higher chance of getting colectomy in 6 months. Reviewing additional clinical data showed cases with more CMV inclusions had a higher percentage of hospitalization, longer hospital stays, and increased steroid usage prior to the specimen collection. Thus, higher the CMV count is the more likely it will cause a CMV infection/disease, instead of being an incidental finding. Luckily, all the CMV many group showed recognizable viral cytopathic effects on H&E alone prior to IHC testing.

The role of CMV infection in IBD and whether treatment is necessary in such patients is still being debated. Some argue that CMV does not affect the long-term prognosis of the underlying disease [25], and others believe that CMV-reactivated UC patients have poor long-term outcomes [26]. In our patient population, 86% of the many group were treated with antiviral therapy compared to only 12.5% of the single group. Furthermore, our data shows that there is no significant difference between hospitalization rates in the single group (37.5%) compared to patients with rare CMV inclusions (21.4%). On the other hand, 100% of patients in the many group required hospitalization and the majority of patients (85.7%) in this group received steroid therapy beforehand.

Thus, CMV infection seems to cause or accompany a worse outcome in IBD patients with severe activity in our cohort. This raises the possibility of single or rare CMV infections in IBD patients could be an innocent bystander. As such, our clinical team didn't probably see any reason to treat them.

Some of the limitations of our studies include the retrospective nature of our study, lack of PCR testing in 87.5% of the single and 78.6% of the rare group. Even though the majority of many group has positive PCR values, having this data for each case could provide a better comparison among the groups. Although, CMV inclusions can be heterogeneously distributed in the tissue and lack of universal PCR testing in the rare and single positive group does not necessarily exclude its biological significance, lack of CMV positivity or fulminant activity in 68% of the follow-up biopsies argue against its persistence or clinical significance in these groups. Similarly, 7% (2 out of 29) of patients did not have any follow-up available in our system, which makes it harder to assess the effects of antiviral treatment.

In summary, this study focuses on the clinical and pathologic correlation of CMV immunostaining in gastrointestinal biopsies of patients with severe IBD to determine whether the CMV IHC is necessary in such population. Our results suggest that CMV infection is rare in IBD patients with severe activity and ulceration. When an abundant CMV infection is present, the viral cytopathic effects should be recognizable by H&E alone. Therefore, H&E should be used as a first line to detect viral inclusions in such patients. In our project, CMV IHC could only help to identify the CMV infection in a minority of cases with no characteristic inclusions on H&E stain. It also should be kept in mind that CMV IHC can help to detect rare or single positive cells; and pathologists should be able to diagnose cases that have many CMV inclusions by thorough evaluation of H&E alone. Further possibly prospective studies are needed to address the CMV biological significance and CMV PCR necessity in suspected patients.

CRediT authorship contribution statement

R. Ertekin: Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **J. Hu:** Investigation. **M. Hosseini:** Validation, Funding acquisition. **C. Patel:** Resources. **V. Vavinskaya:** Supervision, Resources. **M.K. Pezhouh:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Type of study conducted

Single-center, retrospective cohort study.

Declaration of competing interest

The authors declare no conflicts of interest.

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