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DOI: 10.17235/reed.2021.7915/2021
Link: PubMed (Epub ahead of print)

Please cite this article as:
Núñez Ortiz Andrea, Rojas Feria María, de la Cruz Ramírez María Dolores, Gómez Izquierdo Lourdes, Trigo Salado Claudio, Herrera Justiniano José Manuel, Leo Carnerero Eduardo. Impact of Epstein-Barr virus infection on inflammatory bowel disease (IBD) clinical outcomes. Rev Esp Enferm Dig 2021. doi: 10.17235/reed.2021.7915/2021.

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Impact of Epstein-Barr virus infection on inflammatory bowel disease (IBD) clinical outcomes

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Sources of support that require acknowledgment: There are no financial disclosures.

Aknowledgments:

We would like to thank Dr. Maria D Giraldez for her input in manuscript preparation.
This work was presented as a poster at the European Crohn´s and Colitis Organisation Congress, Vienna, February 2020.

Authors' conflicts of interest:

AN has received education funding from Pfizer and Takeda.

MR has received education funding from Abbvie and Ferring.

MDC has received education funding from Ferring and Takeda.

CT have received education funding or has served as speaker from MSD, Pfizer, Abbvie, Takeda, Janssen, Tillotts Pharma, Shire Pharmaceuticals, Ferring, Dr. Falk Pharma and Otsuka.

JMH has received received education funding or has served as speaker from MSD, Pfizer, Abbvie, Takeda, Janssen, Tillotts Pharma, Shire Pharmaceuticals, Ferring and Dr. Falk Pharma.

EL have received education funding or has served as speaker from MSD, Pfizer, Abbvie, Takeda, Janssen, Tillotts Pharma, Shire Pharmaceuticals, Ferring, Dr. Falk Pharma and Otsuka.

Abstract

Objective: To evaluate the role of Epstein-Barr virus (EBV) on the intestinal mucosa in the evolution of inflammatory bowel disease (IBD), to investigate the risk factors for EBV infection and the frequency of EBV-associated lymphoproliferative disorders in IBD patients.

Methods: Intestinal biopsies of IBD patients with available EBV status determined by Epstein-Barr-encoding RNA (EBER) *in situ* hybridization were searched in the Pathology Database of our center.

Clinical information, including phenotypic characteristics of IBD, previous treatments, diagnosis of lymphoma, and patient outcome, were reviewed for all cases.

Results: 56 patients with IBD (28 Crohn´s disease, 27 ulcerative colitis and one unclassified colitis) were included. EBV in intestinal mucosa was positive in 26 patients (46%), in one case associated to a lymphoproliferative syndrome. EBV positivity was associated with severe histological activity (52% *vs.* 17.2%; p 0.007), presence of a lymphoplasmacytic infiltrate (50% *vs.* 33.3%; p 0.03) and active steroid treatment (61.5% *vs.* 33.3%; p 0.03). Multivariate analyses only found association between EBV and lymphoplasmacytosis (p 0.001). Escalation in previous treatment was significantly more frequent in the EBER+ group (53.8% *vs.* 26.7%; p 0.038). No cases developed

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lymphoma in the follow-up.

Conclusions: EBV on the intestinal mucosa is associated with a poor outcome of IBD and the need for escalation in therapy. Lymphoplasmacytic infiltrate is associated with EBV infection. EBER+ patients used steroids more frequently compared with EBER- patients. No EBER+ patients developed a lymphoma during follow-up.

Keywords: Inflammatory bowel disease, Epstein-Barr virus, lymphoplasmacytosis, immunosuppressants, EBER *in situ* hybridization

Introduction

Inflammatory bowel disease (IBD) is characterized by recurring episodes of intestinal inflammation. The pathogenesis is not completely elucidated, but it seems to occur in genetically susceptible individuals due to a dysregulated immune response to luminal antigens, such as bacteria and virus infection. Among them, the Epstein-Barr virus (EBV) has been proposed as a trigger for IBD (1,2).

Upon primary infection, EBV establishes a latent infection in B cells, but under some stimulus, it can react and lead to viral replication (lytic phase) (3-5). In immunocompetent individuals, the immune system identifies the reactivation and eliminates the EBV infected cells in the lytic phase, but under immunosuppression, the virus can escape host immunological surveillance (4). A viral tropism toward sites of active inflammation has been suggested, which would perpetuate the inflammatory process (5,6).

Different studies have shown that EBV prevalence on the intestinal mucosa of IBD patients is higher than in controls, especially in inflamed mucosa and in symptomatic patients. These data suggest a potential role of EBV in triggering the immunologic response (2,7-9). The higher inflammatory burden could condition a poor evolution of the IBD with an increased refractoriness rate to the treatments and, a greater need for surgical interventions (10,11). EBV presence has also been related to the development of lymphoproliferative disorders (3,4,7,12).

Treatment in IBD patients infected by EBV is also controversial. Some authors recommend immunosuppressants withdrawal, whereas others suggest an intensification of the immunosuppression or even addition of antiviral drugs (13-15).

Therefore, we proposed the present study aimed to evaluate the influence of EBV on the evolution and prognosis of IBD. We also investigated the risk factors for EBV infection and the number of EBV-associated lymphoproliferative disorders in our cohort.

Methods

Study population

We searched for IBD intestinal biopsies where EBV was specifically tested from 2009 to 2017 using the hospital Pathology Data System. We only included EBV testing of endoscopically obtained samples. Surgery specimens were excluded as colectomy implied a poor outcome of the disease.

IBD was diagnosed based on Lennard-Jones criteria (16). Endoscopic biopsies were obtained from inflamed areas, except in 2 patients in endoscopic remission, in which case they were taken randomly. EBV testing on the intestinal mucosa was performed by a pathologist in cases with severe inflammatory colitis and/or refractory IBD. In patients with refractory disease, CMV was also tested. In situ hybridization (ISH) for Epstein-Barr virus-encoded RNA (EBER) test was performed using Ventana INFORM EBER Probe and ISH iView blue detection kit on a Ventana BenchMark automated immunostainer following the manufacturer's recommendations (***Image 1***).

Study variables

Demographic and clinical information, including gender, smoking habit, type and phenotypic characteristics of IBD, previous and current immunesupressive and surgical treatments were collected from the electronic medical records. Clinical, endoscopic, and histological activity of IBD at the time of EBER analysis, changes in therapy after EBV diagnostic, diagnosis of lymphoma were reviewed for all cases.

The Mayo Clinic score for ulcerative colitis (UC) and the Harvey-Bradshaw score for Crohn´s disease (CD) patients were used to evaluate clinical activity. The Mayo

endoscopic subscore for UC and the Simple Endoscopic Score for CD were used to classify endoscopic activity. The presence of lymphoplasmacytosis and the histological activity were assessed by a gastrointestinal pathologist. We defined poor evolution of IBD as a requirement of treatment modification (immunosuppressant or biological switch due to lack or loss of response to treatment) or need for hospital admission or surgery related to disease. We also collected if the patients developed a lymphoproliferative syndrome during the follow-up.

Statistical analysis

The qualitative variables are presented using descriptive statistics and were analyzed using the Chi-square or Fisher's test as appropriate. For the quantitative variables, the statistics of centralization and dispersion were calculated; mean and standard deviation or median and interquartile range (IQR) depending on these variables followed a normal distribution (Kolmogorov-Smirnov test), and the Student's t-test/ANOVA or non-parametric tests (U Mann-Whitney) were used, as appropriate. Statistical significance is considered a value of $p<0.05$. Regression methods were used for multivariate analysis.

Legal and ethical considerations

The study was performed in accordance with the principles and ethical standards contained in the Declaration of Helsinki and in accordance with current legal regulations (Royal Decree 223/2004). The study protocol was approved by the Ethics Research Committee in our hospital.

Results

A total of 56 IBD patients in whom the presence of EBV on their intestinal mucosa had been evaluated were included whose baseline characteristics are shown in ***Table 1***.

The average duration of IBD at the time of EBV determination was 59 months. In 11 patients was determined on the debut biopsies. All the patients presented endoscopic activity, this being moderate-severe in 71% of them. Likewise, histological activity was also moderate or severe in 88.9%. Of these, in 32 patients a significant

lymphoplasmacytic infiltrate was described. At the time of EBV determination, 60.7% of patients were receiving immunosuppressive therapy in monotherapy, while 32.1% and 17.8% were under double and triple immunosuppression (***Table 1***).

EBV was positive in 26 patients, one of them associated with a lymphoproliferative syndrome. Of the 11 patients in whom EBV was determined at the debut of the disease, 5 were EBER+. CMV was tested in 54 patients, being positive in 4. Up to 69% of the patients with significant lymphoplasmacytosis were EBER+, whereas EBV was only present in 4 cases without this histological finding (***Figure 1***).

Factors involved in the presence of EBV

The presence of EBV on the intestinal mucosa was associated with a severe histological activity (52% *vs.* 17.2%, p=0,007; OR 5.2 [95% CI 1.5-18]) and the presence of a prominent lymphoplasmacytic infiltrate (84.6% *vs.* 33.3%, p<0.0001; OR 11 [95% CI, 2.9-40.6]). Clinical activity (88.5% *vs.* 66.7%, p 0.08) and severe endoscopic activity (50% *vs.* 33.3%, p=0.21) were more frequent in EBER+, without reaching statistical significance **(*Table 2*)**.

Regarding active treatments, steroid use was significantly more frequent in EBER+ (61.5% *vs.* 33.3%; p=0.03; OR 3.2 [CI 95%, 1.07-9.5]). Neither the use of immunosuppressants nor biologics were associated with an increased risk of EBV; however, the risk was higher when both were used in combination or even in triple immunosuppression.

In the multivariate analysis, the lymphoplasmacytic infiltrate was the only variable independently associated with the presence of EBV (p=0.001).

Therapeutic management after a positive EBV determination.

At the time of EBV determination, no therapeutic change was made in 69.2% of EBER+. In 2 patients, immunosuppression was increased and, in 6 (23.1%) decreased. In 66.6% of EBER-, the same treatment was maintained, and in the rest was intensified (***Figure 2***). Only 5 patients, all EBER+, were treated with antivirals, 4 of them due CMV coinfection.

Influence of EBV in IBD evolution.

The mean follow-up time after EBV determination was 53.3 ± 26.3 months [0-106]. Up to 46.6% of the patients needed changes in IBD treatment, being significantly more frequent in the EBER+ (65.4% *vs.* 30%, p=0.008; OR 4.4 [IC 1.4-13.5]). EBER+ escalated in treatment more frequently than EBER- (53.8% *vs.* 26.7%, p=0.03) during follow-up, including start or switch of immunosuppressants (38.5% *vs.* 6.7%, p=0.004), biologics (46.1% *vs.* 23.3%, p=0.07) or both (34.6% *vs.* 3.3%, p=0.003). Five out of 6 EBER+ patients whose treatment was initially de-escalated subsequently required intensification. In 55% of EBER+ whose treatment was not modified at baseline, it was intensified during follow-up, compared to 30% of EBER- (p=0.11).

Hospital admission and surgery rates were also higher in the EBER+ (38.5% *vs.* 23.3% and 19.2% *vs.* 10%), although without statistical significance. Furthermore, 5/8 patients who underwent IBD-related surgery were EBER+ (***Figure 2***).

No patient developed a lymphoma during the follow-up period. Two EBER+ patients died due to a lung adenocarcinoma and a renal neoplasm, respectively.

Discussion

In this study, we have shown that EBER+ patients have a worse evolution of IBD compared to EBER- patients, requiring escalation in treatment more frequently. Our observation is consistent with prior studies although, unlike them, our population was practically composed of IBD patients with endoscopic or histological activity.

Few studies in clinical practice have analyzed the influence of EBV on the evolution of IBD. In fact, this is the first study to describe detailed therapeutic modifications at the time of EBV diagnosis and in follow-up, including immunosuppressants changes, hospital admission and surgery rates.

EBV and CMV infections can affect the colon, so it can be difficult to distinguish between an outbreak of disease and viral colitis (6,13,17). EBV infection on intestinal mucosa has been reported in up to 64% of patients with IBD (6,18). The presence of CMV is usually tested on IBD mucosa, but EBER ISH is infrequently performed, making the presence of EBV likely underestimated in the usual clinical practice.

Inflammatory activity and immunosuppressive therapy have been proposed as risk factors for the presence of EBV on the intestinal mucosa of IBD patients. It is not defined whether EBV is the cause of the inflammation, uses it to multiply innocently, or this circumstance perpetuates the inflammation. Similarly, it is also unclear if the presence of EBV is associated with immunosuppressive treatment or if this therapy is more frequently used due to the increased activity of IBD (17,18).

Regarding inflammatory activity, a great number of patients presented significant histological activity in our study, mainly in EBER+. One of the histological characteristics was the presence of a lymphoplasmacytic infiltrate that was present in most EBER+, being the only independent risk factor associated with EBV infection in our cohort. This observation was already reported by Nissen *et al*., in which in addition to lymphoplasmacytic infiltrate, the presence of atypical B lymphocytes was associated with a higher prevalence and load of EBV (18). Therefore, in the presence of a lymphoplasmacytic infiltrate on the intestinal mucosa, it is recommended to perform techniques for EBV detection.

The presence of EBV has been correlated with the immunological situation, with a higher prevalence in immunosuppressed patients (14). Contrary to what one might think, thiopurines were not the drugs most related to the presence of EBV but corticosteroids (6,18,20) or anti-TNF (6,18,21,22,23). In our study, the use of steroids is higher in EBER+, which in turn would indicate disease activity. Although neither the use of immunosuppressants or biologics is associated with the presence of EBV, the double or triple immunosuppression increased the risk, probably due to the loss of immune surveillance that would favor EBV replication and proliferation. However, it would not explain the presence of EBV *per se*, since in our study 5 patients were EBER+ at the debut of the disease and, therefore, had not received any immunosuppressive treatment.

The role that EBV in the evolution of IBD has also been discussed. It has been proposed that EBV would complicate the course of the disease by increasing severity, relapses, refractory treatment, and even the rate of colectomies (6,14,18). Pezhouh *et al.* showed a positive association between EBV intestinal infection and refractory IBD (40/67, 60% *vs.* 3/12, 25%) (15). Nissen found that up to 31% of patients with EBV

required surgery. Moreover, the group that underwent surgery presented a higher viral load (18). In our series, the EBER+ group required further therapeutic modifications in follow-up compared to the EBER-, which suggests a more refractory disease. However, these data are biased because treatment was generally escalated in EBER- and de-escalated in EBER+ at baseline. Despite this, the EBER+ patients in whom we did not make any changes at baseline, the need to progress in treatment during follow-up was more frequent. Moreover, the risk of surgery and hospital admission, which was practically double in EBER+ patients. Therefore, a worse evolution can be deduced in the presence of EBV, it would also play a role in the inflammatory process and therapy refractoriness.

Finally, one important complication is the development of a lymphoproliferative syndrome. Most IBD-related lymphomas develop at sites of active intestinal disease in patients with long-standing disease (24) and are associated with thiopurines. In some studies, it has been recommended to withdraw immunosuppressants in patients with EBV-associated lymphoproliferative disease as a step prior to chemotherapy (18). In our series, no EBER+ patients developed a lymphoproliferative disorder during follow-up. One patient presented an EBV-associated lymphoproliferative syndrome at baseline. She had a favorable response after the withdrawal of the immunosuppressants and rituximab treatment.

Among the limitations of our study, it should be noted that this is a retrospective study which may lead to underreporting of cases. In addition small number of patients which would justify the lack of statistical power. Moreover, patients were treated by different physicians with individual therapeutic criteria as the attitude towards immunosuppressive medication in EBER+. Finally, the selection of patients for EBV testing was made by the pathologist based on histological criteria and refractory patients.

In conclusion, EBV on the intestinal mucosa is related to a poor evolution of IBD, with a greater need for escalation in treatment. It is associated with a severe histological activity and the presence of a lymphoplasmacytic infiltrate. No EBER+ patient developed a lymphoproliferative disorder during follow-up. The clinical management of the infection is currently controversial, so prospective studies are needed to address

potential therapeutic measures.

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Table 1. Demographic and phenotypic characteristics at baseline. Clinical and demographic characteristics at the time of EBV determination.

Gender (n, %): Males Females	 35 (62.5) 21 (37.5)
Age at diagnosis of EBV (years, mean ± SD [range])	38.82 ± 14.87 [15-71]
Smoking(n, %):	6 (10.7)
Age at diagnosis of IBD (years, median [IQR])	32 [20-40]
Type of IBD (n, %): Crohn´s disease Ulcerative colitis Unclassified colitis	 28 (50.0) 27 (48.2) 1 (1.8)

Montreal classification of CD (n,%):	
A1 (≤ 16 years)	9 (32.1)
A2 (17-40 years)	16 (57.1)
A3 (> 40 years)	3 (10.8)
Site of disease(n, %)**:**	
L1 (ileum)	2 (7.1)
L2 (colon)	7 (25.0)
L3 (Ileum/colon)	16 (57.1)
L3 + L4 (Ileum/colon + upper gastrointestinal tract)	3 (10.7)
Behaviour(n, %)**:**	
B1 (inflammatory)	23 (82.1)
B2 (stenosing)	2 (7.1)
B3 (penetrating)	3 (10.8)
Perianal involvement(n,%)	11 (39.3)
UC classification(n, %):	
E1 (rectum)	0 (0)
E2 (left-sided colon)	14 (50.0)
E3 (extensive colon)	14 (50.0)
Previous surgical treatment(n,%)	9 (16.1)
CD	8 (28.6)
UC	1 (3.6)
Duration of IBD (months, median [IQR])	59 [11.5-116.75]
Clinical activity n 55(n,%)	
Remission	12 (21.8)
Activity scores:	43 (78.2)
-Harvey-Bradshaw Index (points, mean ± SD)	9.4 ± 3.5
-Partial Mayo score (points, mean ± SD)	5.2 ± 2.5
Endoscopic activity(n,%)	

Inactive	2 (3.6)
Mild	14 (25.0)
Moderate	18 (32.1)
Severe	22 (39.3)
Histological activity n 54(n,%)	
Mild	6 (11.1)
Moderate	30 (55.6)
Severe	18 (33.3)
Concomitant treatment (n%)	
Steroids	26 (46.4)
Immunosuppressants (azathioprine or methotrexate)	25 (44.6)
Biologics	27 (48.2)
Immunosuppressants or biologic	34 (60.7)
Immunosuppressants + biologic	18 (32.1)
Steroids + Immunosuppressants + biologic	10 (17.8)

Table 2. Factors involved in the presence of EBV on the intestinal mucosa.

	EBER + **(N: 26)**	**EBER –** **(N: 30)**	**p**
Male (n, %)	17 (65.4)	18 (60.0)	0,68
Age at diagnosis of IBD (years, median + SD)	33.7 ± 14.0	31.5 ± 15.8	0,58
Smoking (n, %)	4 (15.3)	2 (6.6)	0,57
Type of IBD (n,%)			
CD, N: 28	12 (46.1)	16 (53.3)	
UC, N:28	14 (53.8)	14 (46.6)	0,59
Duration of IBD (months, median + SD)	63.4 ± 12.3	86.3 ± 17.2	0,29
Clinical activity (n, %)	23 (88.5)	20 (66.7)	0,08
Endoscopic activity (n, %)	24 (92.3)	30 (100)	
Mild - Moderate	12 (50.0)	19 (66.7)	

Severe	12 (50.0)	10 (33.3)	0,21
Histological activity (n 54) (n, %)			
Leve - Moderada	12 (48.0)	24 (82.8)	
Grave	13 (52.0)	5 (17.2)	0,007
Lymphoplasmacytic infiltrate (n, %)	22 (84.6)	10 (33.3)	< 0,0001
Concomitant treatment (n, %)			
Steroids	16 (61.5)	10 (33.3)	0,03
Immunosuppressants	12 (46.1)	13 (43.3)	0,83
Biologics	13 (50.0)	14 (46.7)	0,80
Immunosuppressants or biologic	15 (57.7)	19 (63.3)	0,66
Immunosuppressants + biologic	10 (38.5)	8 (26.7)	0,34
Steroids + Immunosuppressants + biologic	6 (23.1)	4 (13.3)	0,27

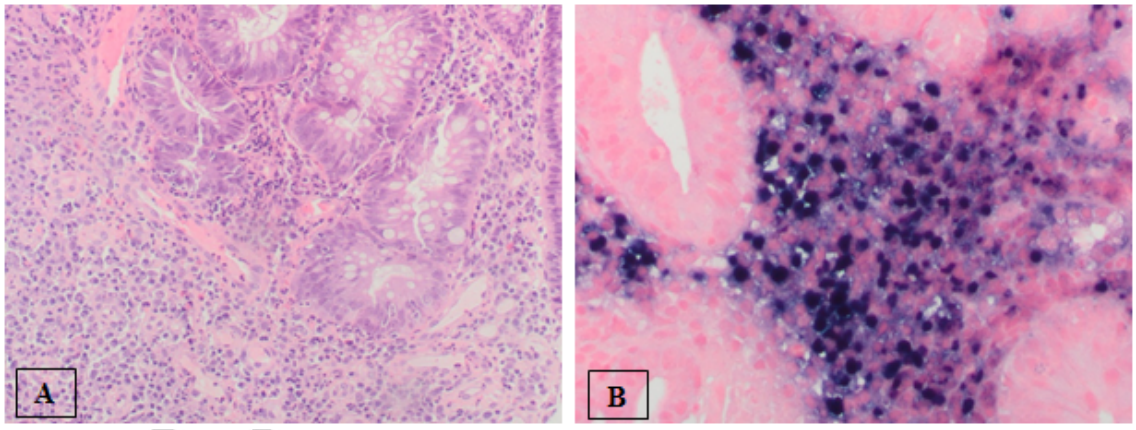

Image 1. A. Lymphoplasmacytic infiltrate. B. In situ hybridization (ISH) for Epstein-Barr virus-encoded RNA (EBER).

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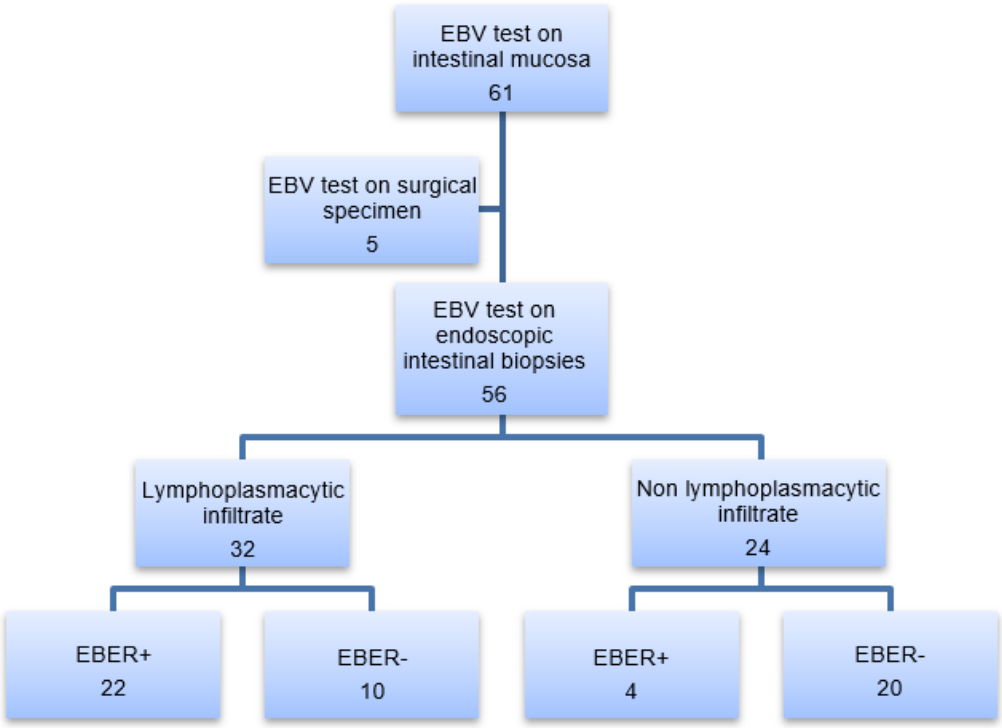
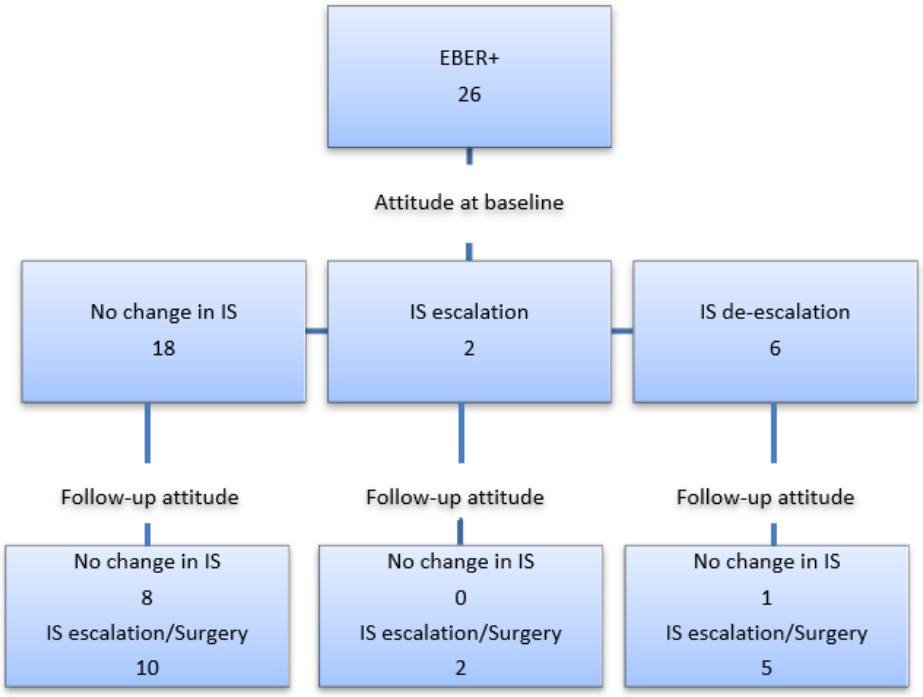
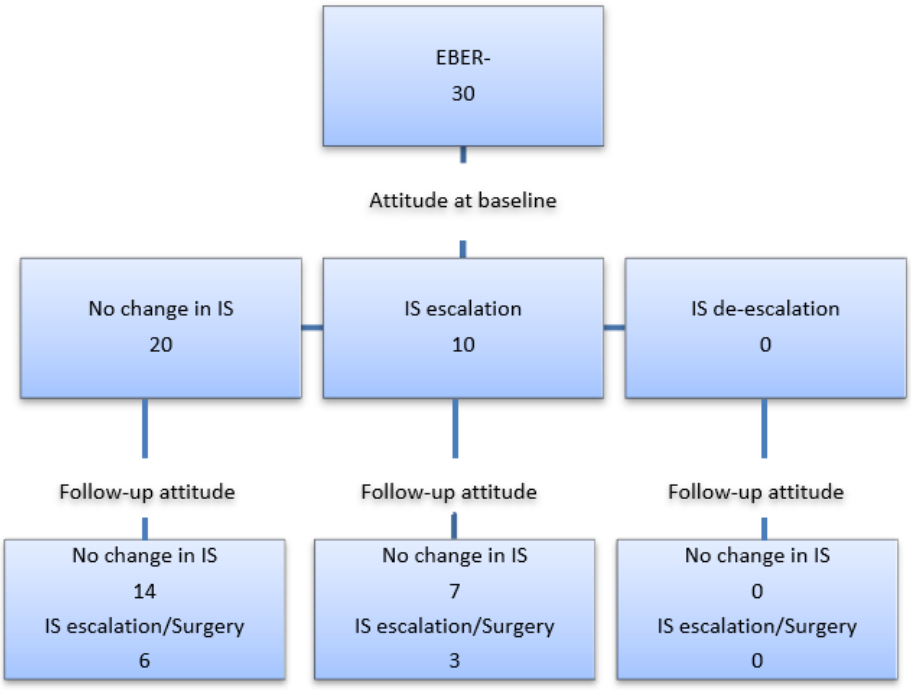


Figure 1. EBV testing on intestinal mucosa. The algorithm shows the cases included and excluded and the EBV status in relation to lymphoplasmacytic infiltrate.





IS: Immunosuppression

Figure 2. Therapeutic attitude at the time of EBV determination (EBER+ *vs* EBER-) and in subsequent follow-up.