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Vascular abnormalities in inflammatory bowel disease in a group of children

Esther Acevedo González,* Carlos Serrano Bello,** Liliana Worona Dibner,* Alejandra Consuelo Sánchez,* Pedro Valencia Mayoral**

RESUMEN

Objetivos: determinar si existen cambios vasculares en biopsias de colon de niños con enfermedad inflamatoria intestinal y describirlos.
Material y método: estudio retrospectivo de control de casos de 16 pacientes con enfermedad inflamatoria intestinal y 32 controles con sangrado intestinal realizado en el Hospital Infantil de México Federico Gómez. Los datos clínicos y los resultados de laboratorio se obtuvieron de los expledientes clínicos; se revisaron las biopsias de colon del Departamento de Patología. Se buscaron: vasculitis, endotelialitis y vasos con pavimentación de leucocitos.
Resultados: los vasos con pavimentación de leucocitos y la endotelialitis predominaron en los casos ($p = 0.03$ y $p = 0.001$), así como la endotelialitis con leucocitos polimorfonucleares ($p < 0.001$) y con células mononucleares ($p = 0.03$); el daño vascular fue extenso en 12 casos y 5 controles ($p < 0.001$); la intensidad global de daño vascular fue severa en 8 casos y 2 controles ($p < 0.001$). En las biopsias de colon de seguimiento se encontraron daño vascular y datos de laboratorio de actividad.
Conclusiones: los cambios vasculares estuvieron presentes de manera significativa en pacientes con enfermedad inflamatoria intestinal; fueron parte de la patogénesis de daño a la mucosa y al mismo tiempo pueden ser indicadores de actividad de la enfermedad.
Palabras clave: enfermedad inflamatoria intestinal, niños, cambios vasculares, vasculitis, endotelialitis, vasos con pavimentación de leucocitos.

ABSTRACT

Objectives: To determine the presence of vascular changes in colonic biopsies of children with intestinal bowel disease (IBD) and to describe them.
Material and methods: This is a case-control retrospective study of 16 patients with IBD and 32 control patients with intestinal bleeding carried on at Hospital Infantil de México Federico Gómez. Clinical data and laboratory results were obtained from clinical charts; colonic biopsies from the Department of Pathology were reviewed. Vasculitis, endothelialitis and pavementing leukocytes vessel were searched.
Results: Leukocyte pavementing vessel and endothelialitis predominated in cases ($p = 0.03$ and $p = 0.001$), as well as endothelialitis with polymorphonuclear leukocyte ($p < 0.001$) and with mononuclear cells ($p = 0.03$), the overall vascular damage was extense in twelve cases and five controls ($p < 0.001$), the overall intensity of vascular damage was severe in eight cases and two controls ($p < 0.001$). In the follow-up colonic biopsies, vascular damage and laboratory data of activity were found.
Conclusions: Vascular changes were significantly present in patients with IBD; they may be part of the pathogenesis of damage to the mucose and at the same time maybe indicators of disease activity.
Key words: intestinal bowel disease, children, vascular changes, vasculitis, endothelialitis, leukocyte pavementing vessel.

* Departamento de Gastroenterología.
** Departamento de Patología.
Hospital Infantil de México Federico Gómez.

Correspondence: Dr. Pedro Valencia Mayoral. Departamento de Patología, Hospital Infantil de México Federico Gómez. Dr. Márquez 162, colonia Doctores, 06720, México, DF.
E-mail: vamp_48@yahoo.com
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During the second half of the twentieth century, a gradual and sustained increase in the incidence of inflammatory bowel disease (IBD) happened, especially ulcerative colitis (UC); this increment is possibly due to an overall augmentation of autoimmune diseases and in the decline of infectious diseases in developed countries, particularly in upper social classes.[1-5] It has been postulated that contact with antigens exposed in intestinal infections may contribute to balance the local immune system response and decreases the risk of

autoimmune diseases; on the other hand an easier access to colonoscopy has contributed to a prompt detection of IBD in pediatric age.[4,6-13] The global incidence of IBD ranges from 2.2 to 6.8 cases per 100,000 children.[3-5,14-16] men are usually more affected with Crohn's disease (CD), while both sexes are equally affected in ulcerative colitis.[1-2,8-9]

There is a genetic predisposition for IBD; both, UC and CD, are polygenic disorders, the involved genes are located on chromosomes 3, 7 and 12; the NOD2 (CARD 15) gene of chromosome 16 is associated with CD and apparently chromosomes 2 and 6 would have a stronger link to UC.[6-7,9-10,17-18] The variability of clinical expression and the varied responses to treatment are probably related to the interaction of gene-gene and gene-environment.[6,13-23]

Intestinal luminal barrier integrity may be compromised by genetic and molecular variations, and alterations in mechanism of bowel repair; chronic or recurrent intestinal inflammation results in modulation of the immune system of the mucosa; intestinal inflammation may be induced by products of commensal bacteria in the intestinal lumen[13,21] and/or food antigens,[23] the interaction with the previous mentioned agents and the intestinal epithelial surface through specific receptors and penetration to the mucosa where they interact directly with cells of the immune system, instead of a classical adaptive response by initial production of IgA, the immune response is switched to IgG secretion.[10,13,21-25]

The diagnosis and activity of IBD is based on clinical, endoscopic, radiological and pathological criteria. Histopathological criteria of intestinal damage are well described, however we have not found any description on vascular changes as part of the microscopic findings of IBD; in CD there have been postulated an underlying vascular disorder[26] which affects predominantly large vessels of the gastrointestinal tract. Extraintestinal vascular damage such as perivascular inflammation and chronic inflammatory and/or granulomatous cell infiltrates with interruption of the internal elastic fiber leading to obliterative vasculopathy, has been associated to IBD;[1-3,6,8-10,12,27-35] also, a primary vasculitis may affect patients with CD.[26]

Vascular changes are a regular feature of autoimmune disease; vasculitis in the digestive tract is a common histological change observed in autoimmune diseases.[26-36] Therefore, if IBD is an autoimmune disorder its vascular changes in the colon biopsies of patients with this disease could be found.

The purpose of this study was to determine and describe the presence of vascular changes in the endoscopic colonic biopsies of children with IBD and compared them with those of the colonic biopsies from patients with colonic polyposis and allergies colitis.

PATIENTS AND METHODS

This is a case-control retrospective study; colonic biopsies of all patients with IBD and controls (two per case) carried intestinal bleeding and managed at Hospital Infantil de México Federico Gómez during January 1996 to July 2007, were included. Demographic, clinical and laboratory tests were obtained from clinical charts; colonic biopsy slides that were obtained from the Department of Pathology were reviewed.

Control group was conformed by thirty-two patients without IBD but with intestinal bleeding due to large bowel poliposis or food allergy. Control patients were also managed in the same period of time. Biopsies were evaluated by two pathologists blinded to the diagnosis.

The vascular changes were assessed according to the following definitions:

a) Leukocytes vascular pavementing (LVP): Transmural migration and adhesion to vascular endothelium of polymorphonuclear (PMN) or mononuclear (MN) to the wall of the vessel without histological evidence of endothelial or mural damage.[26-37]
b) Endothelialitis: Swelling of endothelial cells associated with infiltration of leukocytes in the wall of vessels, intermingled with endothelial cells.[26,33,37]
c) Vasculitis: Inflammatory cells around and within venules with injury of the endothelial cells, picnosis, detachment, cariorrhesis and fibrinoid necrosis of the wall of vessel.[36]

Both, endothelialitis an vasculitis intensity were graded as follows: Mild: Less than one third of the vascular perimeter affected.

Moderate: Up to two thirds of the vascular perimeter affected.

Severe: More than two thirds of the vascular perimeter affected. Extension of LVP, endothelialitis and vasculitis were graded as follows:

Grade I: When one or two vessels were involved.
Grade II: When three or four vessels were involved.
Grade III: When five or nine vessels were involved.

Grade IV: When more than ten vessels were involved. Inflammatory cells type were recorded as follows: Predominant polymorphonuclear (PMN): When more than two thirds of the inflammatory cells were neutrophils or eosinophils. Predominant mononuclear (PMN): When more than two thirds of the inflammatory cells were lymphocytes or plasm cells. Mixed: When both cell types, PMN and MN were equally present. Overall extension of histological damage was graded as follows:
Grade 0: Without vascular lesion in the slides reviewed. Grade I: Up to one fourth of the slides reviewed. Grade II: Up to half of the slides reviewed. Grade III: Up to three quarters of the slides reviewed. Grade IV: Lesion in more than three quarters of the slides reviewed.

Overall intensity of vascular damage was evaluated as follows: Mild: When up to half of the fields reviewed were affected.Moderate: When up to three quarters of the fields reviewed were affected. Severe: When more than three quarters of the fields reviewed were affected

Cases were divided in two subgroups: Symptomatic and asymptomatic. When there were discrepancy between the histophatological grade, the slides were evaluated simultaneously by both observers. Square chi, Fisher's exact test with $\alpha = 5\%$ were used in statistical analysis.

RESULTS

We found sixteen patients with IBD, three had Crohn's disease and thirteen ulcerative colitis; five with allergic colitis, four with familiar polyposis and twenty-three with inflammatory polyps.

Socio-demographic data are shown in Table 1; ten patients with IBD were women and eighteen control patients were also female ($p = 0.06$). Age averaged 7.5 years for cases and 5.7 years for controls. Sixteen patients with IBD come from urban and suburban areas, and none from rural areas, while controls, were from rural areas twelve, and twenty from suburban or urban areas ($p = 0.005$). Ten cases had family history of autoinmune disease, and two other cases of IBD had brothers with allergy; only nine control patients had family history of an allergic disorder.

Histopathological findings: Microscopic vascular changes were observed in all cases since the initial colonic biopsy and in twenty-one control patients ($p = 0.036$). No statistical differences were found between CD and UC. In Figure 1 we can see that endothelialitis and PLV, were the predominant changes found in cases ($p = 0.03$ and $p = 0.001$, respectively). Leukocyte pavementing of polymorphonuclear is shown in figure 2A and 2B; mononuclear pavementing can be observed in 2C; PMN and MN pavementing is shown in figure 2D. Endothelialitis with polymorphonuclear was present in 14 of 16 cases and in 7 of 32 control patients ($p < 0.001$). The intensity of endothelialitis was mild in fourteen cases and nine controls ($p < 0.001$), moderate in seven cases and one control patient ($p < 0.001$); grade III of intensity of endothelialitis were observed in two cases and zero controls, and grade IV only in three cases. In nine cases and eight controls endothelialitis was of mononuclear type ($p = 0.03$), in terms of intensity and extension, no difference was found ($p = 0.74$) between cases and controls.

The overall extension of vascular damage was grade IV in twelve of sixteen cases and in four of 32 controls ($p <$

Table 1. Clinical data

	IBD (n=16)	*Controls (n=32)*	*p*
Age (average)	7.5 years	5.5 years	
Gender female	10	18	NS
Origin			
Rural	0	10	0.002
Urban and suburban	16	22	
Family history	10	11	0.04
Intestinal bleeding	16	31	NS
Abdominal pain	14	13	0.002
Diarrhea	14	7	< 0.001
Weight loss (>20%)	8	2	< 0.001
Fever	6	1	0.003
Arthralgia	6	0	<0.001
Orals ulcers	1	0	NS
Malnutrition	12	8	0.05
Growth retardation	6	8	NS
ESR increased	14	8	< 0.001
Anemia	13	13	0.006
Hypoalbuminemia	13	5	< 0.001
PCR increased	6	1	0.003
Thrombocytosis	5	3	0.05
Hypoproteinemia	4	3	< 0.001

ESR: erytrocyte sedimentation rate; PCR: protein C; NS: not significant.

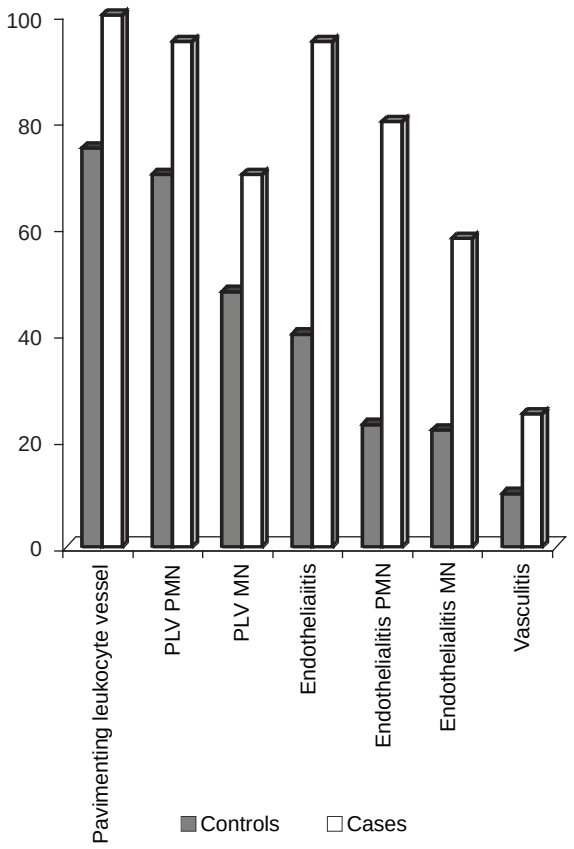

Figure 1. Vascular abnormalities.
MN: mononuclear; PMN: polymorphonuclear; PLV: pavementing leukocyte vessel.

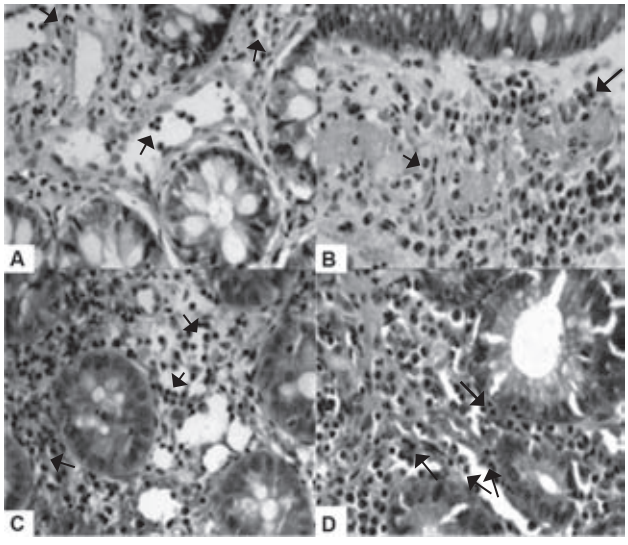

Figure 2. Panels A and B shows polymorphonuclear pavimenting in venules; lymphocyte pavimenting is observed in C and in D pavimenting of PMN and MN and endothelial damage is shown.

0.001). The overall intensity of vascular damage was severe in eight cases and only in one control patient ($p < 0.001$).

Endoscopic follow-up: Subsequence colonoscopies with a four months to one year interval were practiced to thirteen cases; four of them were asymptomatic, the rest persisted with intestinal bleeding only; all patients with or without symptoms showed persistent accelerated erythrocyte sedimentation rate (ESR).

Histopathological findings in subsequent colonic biopsies: Vasculitis as shown in Figure 3A, 3C and 3D was found in three of nine symptomatic patients in a subsequent biopsy taken four months to one year after the first one. Endothelialitis was observed in ten patients in the subsequent biopsy. In 7 of 9 symptomatic cases graded III overall extension of the microscopic damage were found; all asymptomatic cases presented a grade II overall extension of the histological damage ($p = 0.026$). Vasculitis, endothelialitis and leukocyte pavementing was also found in a third biopsy (taken twelve to twenty four months after the initial one) in four symptomatic and four asymptomatic cases.

There was no discrepancy in the identification of vascular events in terms of extension and intensity of the lesion between the two pathologists. We found discrepancies in seven slides regarding the extension of endothelialitis ($p = 0.93$).

DISCUSSION

All patients with IBD came from urban or suburban areas while none from rural areas which maybe in accordance

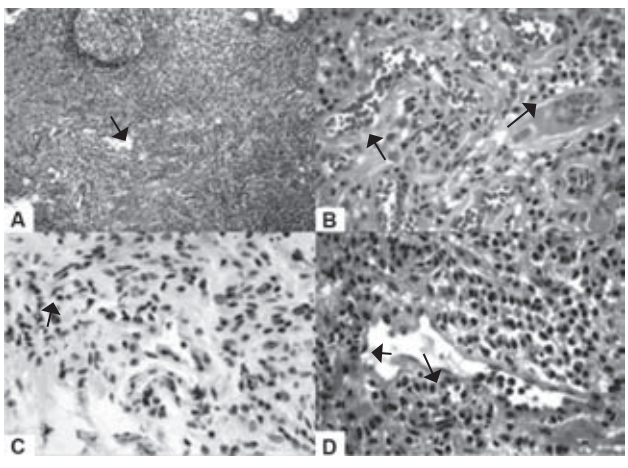

Figure 3. Panel A shows the extension of vasculitis. Panel B displays leukocyte pavimenting affecting vessels. Panels C and D show diverse degrees of vasculitis.

with the theory that propose the lack of exposure to certain infectious agents decreases the expression of autoimmune phenomena in the bowel.[4,10,13,20-23,38]

Some extra-intestinal vascular manifestations of IBD such as thrombosis, arterial occlusion, atherosclerosis and infarcts, have been previously informed,[34-35,39-40] on the other hand, vascular changes may be expected in IBD as occurs in other autoimmune disorders; as far as we are aware, endothelialitis and leukocyte pavementing has not been described in IBD.

We compare our patients with IBD with patients with allergic colitis and colonic poliposis, because they are inflammatory processes as IBD, and share some similar histopathological findings such us mononuclear and polymorphonuclear infiltration of the colonic mucosa, ulcerations and occasionally crypt abscesses,[41-45] although when we compare those findings in our patients, there were statistically significant differences.

Leukocyte pavementing vessel, a change that we observed in all cases, might be produced by mechanisms similar to those proposed for endothelialitis.[4,10,22,40,46-50] In the pathogenesis of IBD, intestinal epithelium, activated cytokines and chemokines production which recruit and activate the cells of intestinal immune system are described; some of these cells were probably recruited from the systemic circulation which would explain leukocyte pavementing. Antigen presenting cells activation or direct stimulation through receptors, promotes Th1 cells differentiation in Crohn's disease, or atypical Th2 in ulcerative colitis.[22,24-25,51-52] The products of Th1 stimulation generate a self-perpetuating activation cycle; in addition to Th1 production of stimulating cytokines (IL-12, IL-18 and inhibiting macrophages migration factor), macrophages produce inflammatory cytokines (IL-1, IL-6 and necrosis tumor factor) which activated a wide variety of cells. The epithelial cells facilitate leukocytes recruitment from vascular space to the mucose, modulating their functional properties.[5,13-15,21,24-25,51-52] Probably leukocytes pavementing can be explained by this mechanism; these functions may be modulated by genetic variants and/or environmental factors.[13-14,24-25,51-52]

Endothelialitis with PMN leukocyte was significantly more often observed in cases; these findings may be explained by activation of lymphocytes of lamina propria: cytokines and chemokines productions which bind to cell adhesion molecules and also have affinity to the endothelium,[33-40,46-48] increases production of mucosal chemotactic agents,[39-40,46] modifications in adhesion molecular expression, changes in the inflammatory cells response to chemotaxis, and increased half-life of PMN leukocyte[33-35] may explain the mucosal infiltration.[10,22,40,47]

Endothelialitis lymphocyte-mediated was also statistically more frequently observed in children with IBD than in controls; their presence may be due to a damage control attempt from the inflammatory process,[4,22-23,48] it has been described that growth factor Tβ (FGT-β) produced by MN is decreased in patients with CD, and increased in UC although in this disorder there is a low sensitivity to FGT-β; therefore a low production or low response to FGT-β may be responsible of mononuclear infiltration.[4,23,49-50,53]

Vasculitis was found in a greater proportion of cases but showed no significant statistical difference. The presence of vascular changes statistically dominant in the group of patients with IBD in colonic biopsies as well as the major overall extension of the lesions in patients with clinically and biochemical active disease lead us to think that vascular changes may be useful in the diagnosis and monitoring activity of IBD. It is worth emphasizing that the vascular changes were observed in both symptomatic and asymptomatic patients and associated with laboratory findings indicative of disease activity. Therefore we propose that vascular changes are significantly present in patients with IBD, they may be part of the pathogenesis of damage to the mucose and at the same time indicators of disease activity.

We had three patients with Crohn's disease in which the histological findings were similar to those observed in UC; however, due to the small number of cases no conclusion could be obtained.

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