IgA vasculitis associated with inflammatory bowel disease.

A retrospective cohort study

Michel Villatoro-Villar, M.D., M.S.[1]

Cynthia S. Crowson, Ph.D.[2,3]

Kenneth J. Warrington, M.D.[2]

Ashima Makol, M.B.B.S.[2]

Matthew J. Koster, M.D.[2]

1. Division of Rheumatology, The University of Arizona Arthritis Center, Tucson Arizona, USA
2. Division of Rheumatology, Mayo Clinic, Rochester, Minnesota, USA
3. Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA

Correspondence:

Dr. Michel Villatoro-Villar, Division of Rheumatology, The University of Arizona Arthritis Center, 1501 N, Campbell Avenue, Tucson, AZ 85724-5093. Tel: 520-626-4111; Fax: 520-626-5018. E-mail: villatorovillarm@email.arizona.edu

Abstract

Objective: To describe the baseline characteristics and outcome of a series of patients with inflammatory bowel disease (IBD) and IgA vasculitis (IgAV).

Methods: Patients with biopsy-proven IgAV with IBD were identified retrospectively. Data were abstracted from direct medical chart review. Each IBD-IgAV case was matched to two controls with IgAV but without IBD.

Results: Nine patients were identified (7 Crohn's disease, 2 ulcerative colitis). Mean length of time between IBD diagnosis and IgAV-onset was 17.3±19.9 years. For patients on biologic treatment for IBD, mean length of time between initiation of biologic and IgAV-onset was 3.3±3.8 years. Active IBD at IgAV-onset was present in 56%.

Tumor necrosis factor inhibitors (TNFi) were used for IBD in 89%. At IgAV-onset, 6 patients were on treatment with TNFi; one subsequently discontinued, two switched to another TNFi, and three continued. At last follow-up, three of five patients that remained on TNFi had full resolution of IgAV despite ongoing TNFi use.

No differences were seen between cases with IBD-IgAV and matched non-IBD IgAV controls in regards to development of end-stage renal disease, resolution of hematuria or proteinuria, and time to complete IgAV response.

Conclusion: Baseline characteristics and outcomes of patients with IBD-IgAV are similar to those with IgAV without IBD. Development of IgAV is not limited to patients with clinically active IBD. Whether use of TNFi is related to the pathogenesis of IgAV in some patients with

IBD remains unclear. Further research into the pathophysiologic connection between IBD and IgAV is needed.

Key Words:

IgA vasculitis, Henoch-Schönlein purpura, inflammatory bowel disease, Crohn's disease, ulcerative colitis

Key messages:

- Baseline characteristics and outcomes of IgAV-patients with and without IBD are similar.
- Development of IgAV is not limited to patients with clinically active IBD.
- Favorable outcomes can occur in patients with IBD-IgAV despite ongoing use of TNFi.

Introduction

IgA vasculitis (IgAV) is a small vessel vasculitis characterized by IgA1-dominant immune deposits often affecting skin, gastrointestinal (GI) tract and kidneys. Clinical manifestations include palpable purpura (PP), abdominal pain, GI hemorrhage, arthralgia/arthritis, and glomerulonephritis (1).

Inflammatory bowel disease (IBD) is a group of idiopathic chronic inflammatory intestinal conditions. The two main categories are Crohn's disease (CD) and ulcerative colitis (UC). Extraintestinal manifestations can occur in up to 40% of IBD patients (2). Skin and mucocutaneous lesions are among the most frequently observed extraintestinal manifestations of IBD with oral aphthae, erythema nodosum and pyoderma gangrenosum the most common pathologies seen. Although mucocutaneous abnormalities may parallel IBD activity, these lesions can also antedate IBD diagnosis and have an independent course (3, 4).

Leukocytoclastic vasculitis (LCV) has been reported as an uncommon extraintestinal manifestation of IBD (5). IgAV has also been observed in patients with IBD but is considered rare (6). In some cases it has been hypothesized that treatment with tumor necrosis factor alpha inhibitors (TNFi) may precipitate the development of either LCV or IgAV in patients with IBD; however, this association remains uncertain (7-9). Data regarding the association of the newer non-TNFi therapies and small vessel vasculitis is scant, but ustekinumab has been implicated as a potential causal role in the development of LCV in a patient receiving therapy for psoriasis (10), and vedolizumab has been suggested as a possible precipitant of IgAV in a patient with Crohn's disease (11).

In order to further understand the interaction between patients with IBD and IgAV, we sought to describe the clinical characteristics and outcome of a series of patients with a history both of IgAV and IBD in comparison to a control group of patients with diagnosis of IgAV but no history of IBD.

Methods

Study design

This was a retrospective study performed in accordance with the ethical standards of the Helsinki Declaration and was approved by the Institutional Review Board at the Mayo Clinic, Rochester, Minnesota USA (IRB #17-004520). Data was obtained through direct medical chart review by a physician abstractor.

Patients

Patients with biopsy-proven, new-onset IgAV diagnosed at Mayo Clinic, Rochester, Minnesota between January 1, 1997 and December 31, 2016 were identified (12). Among this cohort (n=243), patients were further evaluated for diagnosis of IBD, either prior to or after diagnosis of IgAV. Patients with IBD and IgAV (cases) were matched to two patients with IgAV but without IBD (controls) based on age, sex and renal function at time of IgAV onset. For patients with IBD, the clinical characteristics leading to diagnosis and treatments used for IBD maintenance were abstracted. In both the IBD-IgAV and the non-IBD IgAV controls, clinical characteristics present at time of IgAV diagnosis were identified as were treatments following diagnosis, response to therapy and outcome at last follow-up. For patients with IBD-IgAV, special attention was focused on the current and recent IBD treatments at the time of IgAV diagnosis. Outcomes of interest were bowel involvement, renal function, development of renal insufficiency,

requirement of dialysis or renal transplantation, and relapse of IgAV symptoms during follow-up.

Definitions

IBD (CD and UC) was diagnosed based on the World Gastroenterology Organisation (WGO) criteria (3). IgAV was diagnosed in accordance with the American College of Rheumatology (ACR) and the European League Against Rheumatism/ Paediatric Rheumatology European Society/Paediatric Rheumatology International Trials Organisation (EULAR/PRINTO/PRES) criteria (13, 14). In all cases, vasculitis was confirmed via skin and/or renal biopsy. Patients with other forms of small-vessel vasculitis, specifically anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis were excluded (12). Among those with ANCA serologies evaluated, patients could have a positive perinuclear ANCA (p-ANCA), which is known to occur in IBD (15), provided myeloperoxidase (MPO) was negative and presence of ANCA-associated vasculitis was clinically excluded. Cytoplasmic ANCA (c-ANCA) and proteinase-3 (PR3) were required to be negative in all patients.

Estimated glomerular filtration rate (eGFR) and stages of chronic kidney disease (CKD) were classified according to the National Kidney Foundation (16). Proteinuria was defined as nephrotic (NP) if >3.5 g/day or non-nephrotic (NNP) if >0.2 g/day but <3.5 g/day in patients >18 years of age or ≥4 mg/m^2/hour but <40 mg/m^2/hour in patients ≤18 years of age. Microscopic hematuria (MH) was defined as >10 red blood cells/high-power field (RBCs/hpf).

At IgAV diagnosis, IBD disease status was defined in accordance with the American Gastroenterological Association definition for active disease if symptoms related to IBD were

confirmed with objective findings from biochemical markers, endoscopic evaluation, or radiologic investigation showing active inflammation (17).

For IgAV, status at last follow-up was classified as: *complete response* (improvement in all baseline clinical manifestations including, if present, reduction of proteinuria to <0.5 g/d, disappearance of hematuria or reduction to <10 RBCs/hpf, and <20% decrease in eGFR from baseline); *partial response* (improvement in at least one-half of baseline clinical manifestations, and in the case of renal involvement, an improvement of proteinuria to <50% of the baseline value, disappearance of hematuria or reduction to <10 RBCs/hpf and <20% decrease of eGFR from baseline); or *non-response* (lack of improvement in any organ system or improvement in less than half of manifestations present at baseline). *Relapse* was defined as reappearance of clinical signs of vasculitis, attributable to IgAV, occurring after a symptom free period of at least one month.

Statistics

Descriptive statistics (percentage, mean, etc.) were used to summarize patient characteristics. Comparisons between cases and controls were performed using chi-square and rank-sum tests. Univariable Cox models were used to compare outcomes between cases and controls. Analyses were performed using SAS version 9.4 (SAS Institute) and R 3.4.2 (R Foundation for Statistical Computing).

Results

Demographic and baseline information

A total of 9 patients with IBD and IgAV were identified; 67% of patients were Caucasian, 6 were male and 3 female. CD and UC were diagnosed in 7 and 2 patients, respectively. The matched group included 18 patients with IgAV but without IBD. Table 1 summarizes the baseline characteristics of the IBD-IgAV cases and non-IBD IgAV controls at time of IgAV diagnosis. Two patients had positive p-ANCA with negative MPO. The remaining 7 patients had negative ANCA serologies.

Inflammatory bowel disease characteristics

The characteristics of IBD at time of diagnosis are summarized in Table 2. Treatment was indicated in all patients at the time of IBD diagnosis; mesalamine (78%) was the most common medication initiated, followed by oral glucocorticoids (GC) (67%) and azathioprine (AZA) (44%). Biologics were eventually required in 8 of 9 patients. The average number of biologics used was 1.7±1.2 per person, with a maximum of 4 different biologic agents in one patient. TNFi were the most frequent biologics used for IBD (8, 89%), of which infliximab was the most common (7, 78%), follow by adalimumab (4, 44%). Non–TNFi biologics used included ustekinumab (2, 22%) and vedolizumab (1, 11%).

Development of IgA vasculitis in patients with inflammatory bowel disease

In all 9 cases of IBD-IgAV, the IBD diagnosis preceded development of IgAV. No cases of IgAV antedating IBD were observed. The mean length of time between IBD diagnosis and IgAV onset was 17.3±19.9 years. Five of the nine (56%) patients with IBD that developed IgAV (Case#1,2,4,7,9), had active IBD disease at the time of IgAV diagnosis. For patients with IBD-IgAV that were on targeted therapeutics, the mean length of time between initiation of biologic

and IgAV-onset was 3.3±3.8 years (range 0-12). Clinical characteristics at the time of IgAV onset are further detailed in Table 2.

Comparison of baseline IgA vasculitis characteristics between cases and controls

No significant differences were seen between cases (IBD-IgAV) and controls (non-IBD IgAV) in regards to clinical characteristics at diagnosis of IgAV (Table 1). Comorbidities were also similar with the exception that non-IBD IgAV patients had a higher body mass index in comparison to patients with IBD-IgAV (33.1±8.6 vs. 25.6±5.9; *P*= 0.03). Recent infection within one month prior to developing IgAV was observed in four patients in the control group and three patients in the IBD-IgAV cases (*P*= 0.54). While the number of infections preceding diagnosis was not significantly different, the type of infection differed with all controls having upper respiratory or viral infections observed whereas among IBD-IgAV cases the 3 infections detected included one upper respiratory infection, one parastomal abscess (Case#1) and one perirectal abscess (Case#7).

Overall, ischemic abdominal symptoms were similar between groups. In the IBD group, abdominal ischemic manifestations were hematochezia/melena in all patients with intestinal symptomatology. None of these patients developed bowel angina, intestinal perforation or volvulus.

Treatment of patients with inflammatory bowel disease with IgA vasculitis

All but one patient had received a TNFi at some point between time of IBD diagnosis and IgAV-onset; however only six patients were actively receiving treatment with TNFi at the time of IgAV onset. One patient (Case#2) treated with infliximab was discontinued at onset of IgAV. Two patients on infliximab (Case#6,7) were switched to another TNFi (adalimumab), but one of

them (Case#7) subsequently required change to certolizumab (due to undetectable drug levels) then ustekinumab for ongoing activity of IBD even though IgAV symptoms resolved with oral GC initiation. Three patients (Case#4,5,8) on TNFi continued on the same agent (2 infliximab, 1 adalimumab) following development of IgAV. One patient on a non-TNFi biologic (vedolizumab) was changed to a different non-TNFi biologic (ustekinumab).

In addition to the above changes, patients with IBD-IgAV were initiated on additional therapies as described in Table 2. Oral GCs were used as first line management in 7 patients, (mean dose 30.7 mg/day) and topical GC in two patients. Mycophenolate mofetil was initiated in concert with oral GC in one patient. Adjunct angiotensin-converter enzyme inhibitors (ACEI) were started at IgAV diagnosis in two patients with proteinuria (Case#3,8).

Outcome

Complete IgAV response in the IBD group was achieved in 4 patients, partial response in 4 patients and non-response in 1 patient. Only 2 patients had ongoing skin lesions at last follow-up (Case#4,6). However, both cases had limited follow-up (<3 months) after IgAV-onset. At last follow-up, the reason for partial/non-response was most commonly low-volume non-dysmorphic microscopic hematuria (n=3) and/or non-nephrotic proteinuria (n=3). Among patients that had initial complete response, no relapses were observed.

Compared to the time of IgAV-onset, only one patient (Case#9) exhibited renal decline leading to a higher CKD stage [baseline eGFR 55 mL/min per 1.73 m^2 (stage G3a), last follow-up eGFR 28 mL/min per 1.73 m^2 (stage G4)]. No patients developed end-stage renal disease or required dialysis. Malignancy was diagnosed in only one patient during follow-up (metastatic duodenal adenocarcinoma), which was also the cause of the only IBD-IgAV death during the study period.

There were no differences between IBD-IgA cases and non-IBD IgAV controls in regards to outcome (Table 3).

Discussion

In this study, we report the largest single-institution case series of patients with IBD and IgAV and the first study comparing outcomes of patients with IBD and IgAV to those with IgAV alone. Beyond case reports, few studies have evaluated the association between IBD and vasculitis, particularly small-vessel vasculitis. Humbert and colleagues have detailed the description of 11 cases with a history of both IBD (4 UC, 7 CD) and ANCA-associated vasculitis (4 eosinophilic granulomatosis with polyangiitis, 7 granulomatosis with polyangiitis) among a cohort of 1,697 patients with ANCA-associated vasculitis in the French Vasculitis Study Group (18). The authors conclude that the association is possible but is exceptional given this combination was observed in only 0.65% of their ANCA-associated vasculitis patients. Similarly, Sy and colleagues reporting on the frequency of IBD and vasculitis from the combined database of the Vasculitis Clinical Research Consortium and the Canadian Vasculitis Research Network, found only 32 patients with diagnosis of both IBD and vasculitis, 8 of which had ANCA-associated vasculitis and only one with IgAV (6). A systematic review by the same authors found an additional 66 reports of confirmed IBD and cutaneous vasculitis, 8 of which were described as IgAV (6).

Although reports of IgAV in IBD appear to be rare, the deposition of IgA containing immune complexes in tissues, particularly kidneys, of patients with IBD may be under-recognized. Indeed, in a retrospective review of 83 IBD patients (45 CD, 38 UC) with native kidney biopsies, Ambruzs and colleagues noted that IgA nephropathy was the most common listed diagnosis in

IBD patients evaluated for renal insufficiency and/or proteinuria (19). When compared to all the other native renal biopsies performed during the same 11-year period for similar indications, the presence of IgA nephropathy was 3-fold greater in patients with IBD (20/83, 24%) versus non-IBD patients (2,734/33,630, 8%) (19). Given all patients in our cohort had evidence of IBD for several years preceding the development of IgAV, it is plausible that chronic alterations of IgA production with subsequent development of IgA auto-reactivity through mechanisms of mucosal impairment may contribute to the co-existence of these conditions and research investigating such a link is warranted.

The development of IgAV in patients with IBD is likely multifactorial and contributions from medications used to treat IBD may be involved. In particular, TNFi used in the treatment of rheumatic diseases appear to have an association with the development of vasculitis, particularly leukocytoclastic vasculitis, which has been documented in multiple case reports and observational studies (20-25). While an association has been observed, TNFi-associated vasculitis is still considered uncommon. Indeed, a nationwide survey of 1200 French rheumatologists and internists identified only 39 cases of TNFi-associated vasculitis, 32 of which had cutaneous manifestations, 2 with confirmation of IgAV (23). Further support of the rarity of TNFi-associated vasculitis comes through use of the Adverse Events Reporting System of the United States Food and Drug Administration where Mohan and colleagues evaluated all patients exposed to etanercept (116,000 patients) and infliximab (344,000 patients) from the time of drug approval to 2002 and found only 35 reports of leukocytoclastic vasculitis, of which only 17 were biopsy-proven (22).

Determination of causality of TNFi in patients developing cutaneous vasculitis can be clinically difficult. Re-challenge with drug provocation testing is often considered the gold-standard for

confirming hypersensitivity response, but is variably performed, particularly if the clinical manifestations attributed to the medication were considered severe or life-threatening. Studies composed predominantly of patients with inflammatory arthritis have demonstrated recurrence of cutaneous vasculitis on re-exposure to the same TNFi in 33-75% of the few patients re-challenged (22-24). A class effect has also been proposed, but not confirmed, due to the return of cutaneous vasculitis in patients with rheumatoid arthritis despite switching to a different TNFi (20, 23). Much less guidance is available regarding the potential causality in patients with the question of potential TNFi-associated IgAV during treatment for rheumatic diseases in general and IBD in particular. Indeed, only three cases of biopsy-confirmed IgAV with subsequent relapse on TNFi re-challenge have been reported; one patient with inflammatory arthritis (etanercept) (22) and two patients with Crohn's disease (both adalimumab) (26, 27).

The current series highlights both the heterogeneity in the clinical characteristics at onset of IgAV as well as the variability in clinical decisions regarding continuation, discontinuation or switching of TNFi in patients with IBD that develop IgAV. IgAV developed in patients both with and without active IBD and in those on and off TNFi. This demonstrates that TNFi are not the sole precipitant for the development of cutaneous vasculitis in patients with IBD and other factors should be considered. While no patients in the current series were stopped and subsequently re-challenged, it is notable that five of the six patients on TNFi at time of IgAV remained on a TNFi; three of which achieved complete remission despite ongoing use. The option of TNFi continuance is of particular importance in IBD given there are fewer non-TNFi targeted therapeutics available for these conditions when compared to patients with other autoimmune diseases such as inflammatory arthritis. Based on the favorable outcomes in this study despite ongoing use of TNFi, it is the authors' suggestion that continuation of TNFi could

be considered for IBD patients developing IgAV on an individual case basis provided measures to manage the acute IgAV symptoms are appropriately undertaken.

The current series is the first study to compare IgAV developing in patients with IBD to those with IgAV without history of IBD. It is noteworthy that there were no significant differences in the baseline clinical characteristics or outcomes between these two groups. While limited in the number of cases, this information provides clinicians with additional understanding on the prognosis of patients with these concomitant disorders.

Although this is the largest, single-institution case-series describing patients with IBD and biopsy-proven IgAV, this study must be considered in context of its limitations. First, the retrospective design limits available data to information documented by providers in a non-standardized format. Second, all patients were seen at an academic referral center resulting in possible selection bias which could limit the generalizability of the study's findings to other populations. Third, due to small number of cases, findings in this study are limited to hypothesis generation and have not been validated.

In summary, IgAV in patients with IBD can occur but is rare. The clinical characteristics and outcomes of patients with IBD-IgAV appear to be similar to those with IgAV alone. Favorable outcomes can occur in patients with IBD-IgAV despite ongoing use of TNFi. Further research into the association of IBD and IgAV is needed.

Funding: This work was not supported by any funding organization.

Disclosure statement: The authors have declared no conflicts of interest regarding this research project.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65(1):1-11.

2. Huang BL, Chandra S, Shih DQ. Skin manifestations of inflammatory bowel disease. Front Physiol 2012;3:13.

3. Bernstein CN, Eliakim A, Fedail S, Fried M, Gearry R, Goh KL, et al. World Gastroenterology Organisation Global Guidelines Inflammatory Bowel Disease: Update August 2015. J Clin Gastroenterol 2016;50(10):803-18.

4. de Oliveira GT, Martins SS, Deboni M, Picciarelli P, Campos LM, Jesus AA, et al. Cutaneous vasculitis in ulcerative colitis mimicking Henoch-Schonlein purpura. J Crohns Colitis 2013;7(2):e69-73.

5. Ko JS, Uberti G, Napekoski K, Patil DT, Billings SD. Cutaneous manifestations in inflammatory bowel disease: a single institutional study of non-neoplastic biopsies over 13 years. J Cutan Pathol 2016;43(11):946-55.

6. Sy A, Khalidi N, Dehghan N, Barra L, Carette S, Cuthbertson D, et al. Vasculitis in patients with inflammatory bowel diseases: A study of 32 patients and systematic review of the literature. Semin Arthritis Rheum 2016;45(4):475-82.

7. Laresche C, Locatelli F, Biver-Dalle C, Nachury M, Heyd B, Koch S, et al. Severe Henoch-Schonlein purpura complicating infliximab therapy for ulcerative colitis. Cutis 2017;99(1):E20-e2.

8. LaConti JJ, Donet JA, Cho-Vega JH, Sussman DA, Ascherman D, Deshpande AR. Henoch-Schonlein Purpura with Adalimumab Therapy for Ulcerative Colitis: A Case Report and Review of the Literature. Case Rep Rheumatol 2016;2016:2812980.

9. Song Y, Shi YH, He C, Liu CQ, Wang JS, Zhao YJ, et al. Severe Henoch-Schonlein purpura with infliximab for ulcerative colitis. World J Gastroenterol 2015;21(19):6082-7.

10. MacArthur KM, Merkel PA, Van Voorhees AS, Nguyen J, Rosenbach M. Severe Small-Vessel Vasculitis Temporally Associated With Administration of Ustekinumab. J Drugs Dermatol 2016;15(3):359-62.

11. Gold SL, Magro C, Scherl E. A Unique Infusion Reaction to Vedolizumab in a Patient With Crohn's Disease. Gastroenterology 2018;155(4):981-2.

12. Villatoro-Villar M, Crowson CS, Warrington KJ, Makol A, Ytterberg SR, Koster MJ. Clinical Characteristics of Biopsy-Proven IgA Vasculitis in Children and Adults: A Retrospective Cohort Study. Mayo Clin Proc. 2019;94(9):1769-80.

13. Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schonlein purpura. Arthritis Rheum 1990;33(8):1114-21.

14. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 2010;69(5):798-806.

15. Lawrance IC, Murray K, Hall A, Sung JJ, Leong R. A prospective comparative study of ASCA and pANCA in Chinese and Caucasian IBD patients. Am J Gastroenterol 2004;99(11):2186-94.

16. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014;63(5):713-35.

17. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017;153(3):827-34.

18. Humbert S, Guilpain P, Puechal X, Terrier B, Riviere S, Mahr A, et al. Inflammatory bowel diseases in anti-neutrophil cytoplasmic antibody-associated vasculitides: 11 retrospective cases from the French Vasculitis Study Group. Rheumatology (Oxford) 2015;54(11):1970-5.

19. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. Clin J Am Soc Nephrol 2014;9(2):265-70.

20. Jarrett SJ, Cunnane G, Conaghan PG, Bingham SJ, Buch MH, Quinn MA, et al. Anti-tumor necrosis factor-alpha therapy-induced vasculitis: case series. J Rheumatol 2003;30(10):2287-91.

21. Sokumbi O, Wetter DA, Makol A, Warrington KJ. Vasculitis associated with tumor necrosis factor-alpha inhibitors. Mayo Clin Proc 2012;87(8):739-45.

22. Mohan N, Edwards ET, Cupps TR, Slifman N, Lee JH, Siegel JN, et al. Leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents. J Rheumatol 2004;31(10):1955-8.

23. Saint Marcoux B, De Bandt M. Vasculitides induced by TNFalpha antagonists: a study in 39 patients in France. Joint Bone Spine 2006;73(6):710-3.

24. Ramos-Casals M, Brito-Zeron P, Munoz S, Soria N, Galiana D, Bertolaccini L, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Medicine (Baltimore) 2007;86(4):242-51.

25. Flendrie M, Vissers WH, Creemers MC, de Jong EM, van de Kerkhof PC, van Riel PL. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther 2005;7(3):R666-76.

26. Rahman FZ, Takhar GK, Roy O, Shepherd A, Bloom SL, McCartney SA. Henoch-Schonlein purpura complicating adalimumab therapy for Crohn's disease. World J Gastrointest Pharmacol Ther 2010;1(5):119-22.

27. Marques I, Lagos A, Reis J, Pinto A, Neves B. Reversible Henoch-Schonlein purpura complicating adalimumab therapy. J Crohns Colitis 2012;6(7):796-9.

Table 1: Baseline clinical characteristics of new-onset IgA vasculitis patients, with and without inflammatory bowel disease

	Non-IBD n=18	IBD n=9	*P*-value
Demographics			
Age (mean, SD)	40.7 (17.4)	40.8 (17.5)	0.96
Sex (male)	12 (67%)	6 (67%)	1.00
Race (white)	16 (94%)	6 (86%)	0.24
Length of follow-up (mean, SD)	1.1 (1.2)	1.3 (2.6)	-
Smoking (ever)	7 (39%)	3 (33%)	0.40
Body mass index, kg/m^2 (mean, SD)	33.1 (8.6)	25.6 (5.9)	0.03
Comorbidities			
Hospitalization	6 (33%)	4 (44%)	0.57
Previous infection	4 (22%)	3 (33%)	0.54
Chronic kidney disease	2 (11%)	1 (11%)	1.00
Hypertension	0 (0%)	1 (11%)	0.15
Abdominal ischemic involvement	2 (11%)	3 (33%)	0.16
Skin involvement	18 (100%)	9 (100%)	-
Lower extremity	18 (100%)	9 (100%)	-
Upper extremity	8 (44%)	4 (44%)	1.0
Abdomen/lower back	9 (50%)	3 (33%)	0.41
Chest/upper back	1 (6%)	0 (0%)	0.47
Ulceration	1 (6%)	0 (0%)	0.47
Renal involvement	10 (56%)	7 (78%)	0.41
Microscopic hematuria	7 (39%)	5 (56%)	0.41
Proteinuria	8 (44%)	7 (78%)	0.10
[a]Non-nephrotic range	7 (88%)	7 (100%)	0.33
Creatinine, mg/dL (mean, SD)	0.9 (0.3)	1.0 (0.4)	0.59

IBD, inflammatory bowel disease; SD, standard deviation

[a]Non-nephrotic proteinuria <3.5 g per 24 hours; urine protein:creatinine ratio <2000 mg/g in children

Table 2: Summary of clinical characteristics of patients with inflammatory bowel disease and IgA vasculitis

	Inflammatory bowel disease					IgA vasculitis				
Case ID	**Sex**	**Diagnosis year & age**	**Prior Treatments**	**IBD treatment at IgAV onset**	**IBD status at IgAV onset**	**Year & age**	**Symptoms of IgAV**	**Labs**	**Lines of Treatment**	**Outcome**
IBD-IgA 01	Female	Crohn's disease 2003 Age: 11	SSZ (2003) GC (2003) 6-MP (2004) IFX (2004) VEDO (2014-2016)	VEDO	Active	2016 Age: 24	PP (LE) Arthralgia	MH: 11-20RBCs/hpf Proteinuria: 291mg/24hrs Cr: 0.5mg/dL	Biologic changed VEDO → UST 1st Oral GC	Partial response -MH -NNP
IBD-IgA 02	Female	Crohn's disease 2001 Age: 14	SSZ (2001-2003) MES (2003-current) 6-MP (2004-2006) GC (2005) IFX (2005-2006)	IFX MES 6-MP	Active	2006 Age: 19	PP (LE) Abd pain N/V/D BRBPR	Proteinuria: 100mg/dL Cr: 0.9mg/dL	TNFi stopped 1st Oral GC, MMF 2nd IVIG MMF → AZA during maintenance	Complete response
IBD-IgA 03	Male	Crohn's disease 1960 Age: 9	-	-	Inactive	2015 Age: 64	PP (LE, UE and abd) Abd pain BRBPR	MH: 51-100 RBCs/hpf Proteinuria: 1478mg/24hrs	1st ACEI, topical GC 2nd Oral GC 3rd Colchicine 4th Dapsone	Partial response -MH -NNP
IBD-IgA 04[a]	Male	Ulcerative colitis 2006 Age: 39	MES (2006-2008) GC (2006-2008) AZA (2008) IFX (2008)	IFX	Active	2011 Age: 44	PP (LE, UE and abd) Arthralgias Abd pain N/V BRBPR	Cr: 0.8mg/dL	TNFi continued (IFX) 1st Oral GC	Partial response -Skin
IBD-IgA 05	Female	Crohn's disease 1988 Age: 18	MES (2003-2005) SSZ (1988-2003) GC (2003) AZA (2003-2009) IFX (2005-2009)	IFX AZA	Inactive	2008 Age: 38	Abd pain PP (LE) Arthralgias (ankles)	MH:3-10RBCs/hpf Proteinuria: 203mg/24hrs Cr: 0.8mg/dL	TNFi continued (IFX) 1st Oral GC	Complete response
IBD-IgA 06[a]	Male	Crohn's disease 2010 Age: 54	MES (2010) IFX (2012)	IFX	Inactive	2013 Age: 57	PP (LE)	Cr: 1.2mg/dL	TNFi changed IFX → ADA 1st Topical GC 2nd Oral GC	No response

IBD-IgA 07	Male	Crohn's disease 2014 Age: 14	MES (2015) GC (2015) AZA (2015) IFX (2015-2016)	IFX	Active	2016 Age: 16	PP (LE, UE) Abd pain N/V/D Arthralgia	MH: 3-10RBC/hpf Proteinuria: 235 mg/24hrs Cr: 0.6mg/dL	TNFi changed IFX→ADA→ CTZ→UST 1st Oral GC	Complete response
IBD-IgA 08	Male	Ulcerative colitis 1993 Age: 23	MES (2007-2015) IFX (2013-2015) ADA (2015)	ADA	Inactive	2015 Age: 45	PP (LE)	MH: >100 RBCs/hpf Proteinuria: 2398 mg/24hrs Cr: 1.8mg/dL	TNFi continued (ADA) 1st Oral GC, ACEI	Complete response
IBD-IgA 09[b]	Male	Crohn's disease 1970 Age: 10	MES (2009) GC (2009) AZA (2009-2012) MTX (2012-2016) Probiotics (2016) CTZ (2009) ADA (2014)	Probiotics	Active	2016 Age: 56	PP (LE, UE and abdomen)	Proteinuria: 539 mg/24hrs Cr: 1.5mg/dL	1st Oral GC 2nd Topical GC 3rd Colchicine	Partial response -NNP

6-MP: 6-mercaptopurine; Abd: abdominal, ACEI: angiotensin-converter enzyme inhibitor; ADA: adalimumab; AZA: azathioprine; BRBPR: hematochezia/melena; CTZ: certolizumab; Cr: creatinine; D: diarrhea; GC: glucocorticoids; IFX: infliximab; IVIG: intravenous immunoglobulin; LE: lower extremities; MES: mesalamine; MH: microscopic hematuria; MMF: mycophenolate mofetil; MTX: methotrexate; N: nausea; NNP: non-nephrotic proteinuria; PP: palpable purpura; RBCs/hpf: red blood cells/high power field; SSZ: sulfasalazine; TNFi: tumor necrosis factor inhibitor; UE: upper extremities; UST: ustekinumab; V: vomiting; VEDO: vedolizumab

[a]Less than 3 month follow-up

[b]Deceased at last follow-up (duodenal adenocarcinoma)

Table 3: Comparison of outcomes between patients with IgA vasculitis without inflammatory bowel disease to patients with IgA vasculitis with inflammatory bowel disease

Outcome	HR	95% CI	*P*-value
Resolution of hematuria	1.83	(0.46, 7.36)	0.39
Resolution of proteinuria	0.98	(0.22, 4.38)	0.98
Time to complete IgAV response	0.88	(0.28, 2.79)	0.83
Mortality	1.33	(0.12, 15.29)	0.82

HR, hazard ratio