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CASE REPORT

Immune thrombocytopenic purpura in ulcerative colitis: a case report and systematic review

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Over 100 extraintestinal manifestations are reported in ulcerative colitis (UC). A commonly reported hematological manifestation is autoimmune hemolytic anemia. On rare occasions, immune thrombocytopenic purpura (ITP) has been reported with UC. The presence of thrombocytopenia can complicate the clinical scenario as the number of bloody bowel movements is an important indicator of disease activity in UC. A proposed theory for this association is antigenic mimicry between a platelet surface antigen and bacterial glycoprotein. We are reporting a case of UC and associated ITP managed successfully with anti-TNF therapy. We also performed a systemic review of case reports and a case series reporting this association.

Keywords: *immune thrombocytopenic purpura*; *ulcerative colitis*; *anti-tumor necrosis factor antibodies*; *intravenous immunoglobulins*; *extraintestinal manifestation*

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A 26-year-old African American female with a history of genital herpes developed hematochezia 6 weeks prior to hospital admission. She was seen at an urgent care center and was prescribed a 1-week course of oral antibiotics. The patient continued to have hematochezia for which she was scheduled to have a colonoscopy as an outpatient. Her hematochezia worsened over the next 2 weeks and she was admitted to an outside hospital where she was managed with a presumed flare of ulcerative colitis (UC) based on clinical diagnosis. The patient was treated with oral steroids and intravenous antibiotics and discharged on a tapering course of steroids for 1 week. During the hospitalization, her platelet count was $236 \times 10^3/mm^3$.

She experienced partial improvement in her symptoms with steroids use, but shortly after stopping steroids her symptoms worsened. She presented to our hospital emergency department with 2 days of 8–9 bloody bowel movements per day, mild left-lower quadrant abdominal pain, no fever or chills but reported a 20 pound weight loss. On admission, her white cell count was $10{,}370/mm^3$, hemoglobin of 11.4 g/dL, and platelet count was $76 \times 10^3/mm^3$. Intravenous methylprednisolone was administered. Her medications were reviewed for possible thrombocytopenia and there was no reported history of alcohol use. HIV and *H. pylori* serology and blood cultures were negative. Colonoscopy showed pan colitis with histopathology consistent with UC without any viral inclusions.

On day 5 of hospitalization, her platelet count decreased to $5 \times 10^3/mm^3$, her frequency of bloody bowel movement increased, and she became febrile and tachycardic. The patient was started on intravenous ciprofloxacin plus metronidazole and intravenous steroids were continued. The peripheral smear showed few large size platelets and the patient did not have splenomegaly. These results suggested the possibility of immune mediated peripheral destruction of platelets. Intravenous immunoglobulin (IVIGg) was administered and one unit of platelets transfused. On days 6 and 7, platelet counts improved to $24 \times 10^3/mm^3$ and $36 \times 10^3/mm^3$, respectively, but the patient continued having bloody bowel movements. Positive platelet-associated antibodies confirmed diagnosis of immune thrombocytopenic purpura (ITP). Because of the lack of response to steroids, Infliximab infusion 5 mg/kg was administered on day 7. On days 8 and 9, frequency of bloody stool decreased significantly and platelet count continued to improve, $94 \times 10^3/mm^3$ on day 9. At that point, the patient was discharged on a tapering dose of steroids and scheduled Infliximab infusion. On outpatient follow-up 10 days after discharge, her platelet count was normal at $151 \times 10^3/mm^3$ and she was free of hematochezia.

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Table 1. Summary demographics and treatment in reported cases

Author	Year	Age	Gender	Race	Medical treatment UC	Additional medical treatment for ITP	Surgical treatment	Comments
Edwards	1964	Adult	–	–	–	–	–	3-cases
Kocoshis	1979	Pediatric	–	–	–	–	–	–
Hautefeuille	1985	20	M	White	Steroid	IVIGg	Splenectomy, colectomy	Good response to surgical intervention
Dooley	1986	63	M	White	Sulfa, steroid	–	Splenectomy	Partial response to steroids, complete resolution of ITP with splenectomy
Gupta	1986	42	M	White	Sulfa, steroid	–	Splenectomy	No response to steroid
Mori	1987	50	F	Asian	–	Steroid	–	Platelet count maintained on 1 mg daily betamethasone
Jimbo	1992	24	M	Asian	Sulfa, steroid	–	–	No recurrence with subsequent flare
Adachi	1994	49	F	Asian	Sulfa, steroid	–	Splenectomy	–
Fernandez-Miranda	1994	22	F	White	5-ASA, steroid	–	Splenectomy	Partial response to steroids, complete resolution of ITP with splenectomy
Obata	1994	13	F	Asian	Steroid	–	–	–
Kim	1995	41	M	White	5-ASA, steroid	IVIGg	Splenectomy	Good response to medical treatment but underwent splenectomy
McCulley	1996	21	F	White	5-ASA, steroid, metronidazole	–	–	–
Yoshida	1996	27	M	White	5-ASA, steroid	IVIGg	–	Chronic thrombocytopenia despite multiple courses of steroids
Yoshida	1996	65	F	White	5-ASA, steroid	IVIGg	–	–
Yoshida	1996	42	F	White	5-ASA, steroid	–	Splenectomy	–
Nagata	1997	19	M	Asian	Steroid	–	–	–
Zlatanic	1997	18	M	White	5-ASA, steroid, 6-MP	6-MP and IVIGg	–	–
Bauer	1999	24	F	White	5-ASA	IVIGg	Splenectomy, Colectomy	Resistant to IVIGg and splenectomy but responded to colectomy
Kodaira	1999	23	M	Asian	Sulfa, steroid	–	Splenectomy	Responded to steroids but reoccurred for which splenectomy was performed
Chetri	1999	42	M	Asian	5-ASA, steroid	azathioprine	–	–
–	1999	52	F	Asian	5-ASA, steroid, azathioprine	–	Splenectomy	ITP preceded UC by 18 years
Higuchi	2001	9	M	–	Sulfa	Anti-D antibodies	–	–
–	2001	17	M	–	Steroid	IVIGg	–	–
–	2001	5	F	–	5-ASA, steroid	Anti-D antibodies, IVIGg	–	Responded will after starting 5-ASA
–	2001	14	M	–	5-ASA, steroid, 6-MP	IVIGg	Colectomy	Recurrent ITP despite colectomy

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(page number not for citation purpose)

Table 1 (*Continued*)

Author	Year	Age	Gender	Race	Medical treatment UC	Additional medical treatment for ITP	Surgical treatment	Comments
Kathula	2001	28	F	–	Steroid	IVIGg	Colectomy, splenectomy	Transient response to IVIGg and splenectomy, complete resolution of ITP with colectomy
Miner	2001	63	F	–	5-ASA, steroid, metronidazole	–	Splenectomy	Splenectomy for recurrence of ITP with steroid tapper
Mizuta	2003	19	M	Asian	5-ASA, steroid	–	Colectomy	–
–	2003	51	F	Asian	5-ASA, steroid	–	–	Patient expired from intracranial hemorrhage
Puebla-Maestu	2003	41	F	White	5-ASA, steroid	Cyclosporine, azathioprine	Colectomy Splenectomy	Not responded well to medical treatment
Varderili	2003	20	M	White	Steroid	–	Colectomy	Partial response to steroids, complete resolution of ITP with colectomy
Hisada	2006	36	M	Asian	Steroid	IVIGg	Colectomy	Good response to IVIGg and complete response following colectomy
Kawakubo	2008	53	M	Asian	Steroid	–	–	ITP preceded UC
Yong	2008	14	M	White	–	IVIGg	–	ITP after colectomy
Shao	2009	19	M	Asian	5-ASA, steroid	–	–	–
Mares	2011	32	M	White	Steroid, Infliximab	IVIGg	–	–
Etou	2013	41	F	Asian	No exacerbation of UC	–	–	ITP resolved on eradication of *H. pylori*
Chandra	2013	26	F	Black	Steroid, Infliximab	IVIGg	–	Patient did not tolerate 5-ASA

ITP: immune thrombocytopenic purpura; IVIGg: intravenous immunoglobulin G; Sulfa: sulfasalazine; UC: ulcerative colitis.

Systematic review

Search and data compilation

A comprehensive search of two major databases of biomedical publications was performed during the last week of August 2013. No age or language restrictions were applied. A summary of our search strategy is described in the Appendix. Titles and abstracts were reviewed to identify cases. The references of eligible articles were hand searched to elicit additional cases. All of the adult and pediatric cases reports and series reporting UC associated with ITP were included. Data points were extracted based on the best information reported.

Results

Cases of ITP associated with UC were first reported in 1963 (1). Since then, a total of 40 cases (including the above-mentioned case) were identified, seven of them being of pediatric age group. Table 1 summarizes patient demographics and management of UC and associated ITP. Fifty six percent of cases were male and the median age of presentation was 27 years (interquartile range 14–42 years). Median age of presentation was higher in females (41 vs. 22 years) but the difference was not statistically significant ($p = 0.0718$). As shown in Table 1, 52% of patients were white, 45% were Asian (mostly of Japanese origin). The current report documents the first case in an African American patient.

In the majority of cases, ITP resolved with treatment of UC flare. IVIGg or anti-D antibodies were used in 15 cases; response was adequate and lasting in 11 of them. Amongst the remaining four patients, one responded dramatically to 5-ASA; in two cases, ITP was resistant to both IVIGg and splenectomy and required a colectomy; and in one case, colectomy and splenectomy were performed together, which improved the ITP. Ten patients underwent a colectomy; one of them had a colectomy some years prior to the development of ITP (2). Of the remaining nine cases, eight responded well but one patient continued to have recurrent ITP despite colectomy (3). In one case, ITP resolved with *H. pylori* eradication (4).

Discussion

The development of ITP adds complexity in the clinical course of UC flare as the number of bloody bowel movements is one of the important criteria to assess disease severity. Since 1965, a total of 40 cases reported association of ITP with UC. Rarity of occurrence limits methodologically sound studies to establish causal relationship between the two disorders. In disease epidemiology, Sir Austin Bradford Hill proposed criteria for causation, also knows has Hill's criteria for causation (5). Results of this systematic review elicit multiple interesting observations to generate a hypothesis of causal relationships between UC and ITP. 1) In most cases, UC preceded ITP, which demonstrates a temporal relationship between UC (exposure) and ITP (effect). Only three cases have been reported where ITP preceded UC (6, 7). In two of the cases, ITP preceded UC by just 18 months. This could be a result of delay in diagnosis or subclinical disease, which is not uncommon in UC. In another case, ITP preceded UC by 18 years, which appears to be a result of random concurrence of the two disorders. 2) Platelet count was lowest during the flare of UC, demonstrating a biological gradient. 3) In most cases, treatment of UC resolved ITP, analogous to the removal of exposure leading to reversal of effect. Biological plausibility in ITP development in patients with UC is hypothesized to be due to antigenic mimicry between platelet surface antigen and luminal antigens, including bacterial surface antigen. Increased exposure to luminal antigens is thought to be the result of mucosal injury. This is also postulated for the association of ITP with Crohn's disease (8).

The results of our systematic review suggest that peak age for this association is in the third decade of life with a trend towards earlier occurrence in males. Cases have been reported in both pediatrics and adults above 60 years of age. About half of the cases were reported in the Japanese population. We report the first case in the African American population. In the management of this coexistence, treatment of UC is the corner stone. In severe cases of thrombocytopenia, IVIGs or Anti-D antibodies in combination with 5-ASA and/or steroids are effective in most cases. These patients should also be screened for *H. pylori*. The infection needs to be eradicated if presented. Refractory cases respond to colectomy and splenectomy but are rarely necessary (4). We are reporting a second case where a colectomy was avoided by using anti-tumor necrosis factor therapy (9).

In conclusion, ITP appears to be an extraintestinal manifestation of UC. The proposed pathogenesis is antigenic mimicry between luminal antigen and platelet surface antigen. Treatment of underlying UC flare is the cornerstone in managing the condition and in severe cases of ITP, IVIGs is effective. Though colectomy has been proposed as a definitive treatment option, the use of biological agents is an acceptable alternative in a steroid-resistant case of UC associated with ITP.

Conflict of interest and funding

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Appendix

Database: Embase <1988 to 2013 Week 34>, Ovid MEDLINE(R) <1946 to August Week 2 2013>

Search Strategy:

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1. Ulcerative colitis.ab. or Ulcerative colitis.ti. or Ulcerative colitis.kw. or Ulcerative colitis.kf. (54,832)
2. Autoimmune thrombocytopenic purpura.ab. or autoimmune thrombocytopenic purpura.ti. or autoimmune thrombocytopenic purpura.kw. or autoimmune thrombocytopenic purpura.kf. (810)
3. Idiopathic thrombocytopenic purpura.ab. or idiopathic thrombocytopenic purpura.ti. or idiopathic thrombocytopenic purpura.kw. or idiopathic thrombocytopenic purpura.kf. (7,469)
4. ITP.ab. or ITP.ti. or ITP.kw. or ITP.kf. (10,614)
5. 2 or 3 or 4 (15,035)
6. 1 and 5 (61)
7. Remove duplicates from 6 (37)