CASE REPORT

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5-ASA Induces Mild Acute Pancreatitis. Case Report and Review of the Literature

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ABSTRACT

5-aminosalicylic acid has been reported to be able of inducing acute pancreatitis as an adverse reaction. However, in most case reports, rechallenge of the drug is missing; therefore, evidence is still needed to confirm its role in the clinical course of acute pancreatitis and its influence on the outcome. Here, we report a case of recurrent acute pancreatitis secondary to 5-aminosalicylic acid, with positive unintentional rechallenge. A systematic search of the literature was performed and 42 cases from 35 articles were summarized concerning the clinical course of 5-aminosalicylic acid induced acute pancreatitis.

Key words: acute pancreatitis – 5-ASA – 5-aminosalicylic acid – rechallenge – drug-induced – adverse drug reaction – Crohn's disease.

Abbreviations: 5-ASA: 5-aminosalicylic acid; AP: acute pancreatitis; CRP: C-reactive protein; CMV: cytomegalovirus; HIV: human immunodeficiency virus; HHV: human herpes virus; ERCP: endoscopic retrograde cholangiopancreatography; DIAP: drug-induced acute pancreatitis; MRCP: magnetic resonance cholangiopancreatography; ADR: adverse drug reaction.

INTRODUCTION

5-aminosalicylic acid (5-ASA: mesalazine, mesalamine) is an aminosalicylate anti-inflammatory drug considered safe and effective in treating inflammatory bowel disease. Frequent side effects are diarrhea, abdominal pain, nausea, vomiting, bloating, headache and allergic skin rash. Acute pancreatitis (AP) is listed as rare in occurrence but is potentially lethal in severity. Pentasa® is an ethylcellulose-coated, granulated, time-dependent, prolonged-release preparation manufactured for balanced absorption of the active component, 5-ASA. However, several cases have been published reporting AP as a consequence of the therapy with 5-ASA-derived drugs [1-5]. Here, we report a case of recurrent AP secondary to 5-ASA, proven with positive rechallenge and a systematic review of the literature in this topic. We strictly followed the CARE guideline recommendations [6] to ensure the highest quality.

CASE REPORT

A 31-year-old white female presented to the Emergency Department at the University of Pécs, Hungary, with vomiting and severe cramping abdominal pain located to the left kidney and radiating to the back and the epigastric region.

Her medical history revealed mitral valve prolapse, multiple episodes of pneumothorax, cured with an atypical apical pulmonary resection. The patient was non-smoker, consumed alcohol occasionally, and denied taking illicit drugs. She had known allergies to trimethoprim and lactose, and family history was significant for hypertonia in her father and multiple sclerosis in her mother.

Six weeks prior to this index admission, she was diagnosed with colonic Crohn's disease and started on granulated 5-ASA (Pentasa®) in a dose of 2000 mg oral daily.

Two weeks prior to this admission she had been admitted for abdominal discomfort, bloating, persistent diarrhea and chest pain. An exacerbation of Crohn's disease was assumed. 5-ASA was temporarily discontinued and methylprednisolone was added to her treatment. Abdominal ultrasonography

showed normal findings. Pneumotorax, pulmonary embolism and pneumonia were excluded. 5-ASA was reintroduced with a dose of 4000 mg and she was discharged. Figure 1 presents a brief illustration of the clinical course.

On current presentation, her abdomen was tender on palpation. The serum pancreatic amylase (295 U/L, normal: 28–100 U/L), and lipase levels (1455 U/L, normal: <60 U/L) were elevated. The levels of inflammatory parameters were increased with a C-reactive protein (CRP) value of 16.60 mg/L (normal < 5 mg/L) and a white blood cell count of 41,300 G/L (normal: 4000–10000 G/L). On abdominal ultrasound the pancreas had normal echogenicity and echostructure, there were no stones in the gall bladder and no dilation of the common bile duct. A moderate wall thickening was present throughout the colon as a manifestation of Crohn's disease.

Acute pancreatitis (AP) was diagnosed, and the patient was treated according to the evidence-based practice guidelines [7, 8]. She was given intravenous hydration, early nasogastric tube feeding, intravenous drotaverine (40 mg), tramadol (50 mg) and metamizole (1000 mg) for pain management, and ondansetron (4 mg) for nausea. 5-ASA was discontinued immediately. She was not aware of any AP episodes before. No calcifications were detected in the pancreatic tissue on ultrasound. The serological tests showed a previous infection with Epstein–Barr Virus and the effect of vaccination against mumps and rubeola; active infections with CMV, Varicella-zoster, HIV1 and 2, Hepatitis A, B, and C, HHV and Adenovirus were excluded. No pathogenic PRSS1 mutations were found on genetic testing for predisposing factors of pancreatitis. Her calcium and triglyceride serum levels were in the reference range. No signs of vascular disease were found. No recent trauma occurred, and no surgical interventions or ERCP was performed. Hence, the diagnosis was idiopathic AP.

Amylase and lipase levels began to drop immediately after starting the treatment and the epigastric pain subsided on day two. Amylase level dropped to normal (45 IU/L), and the levels of lipase and inflammatory parameters progressively decreased. Since the first episode of AP was considered as idiopathic, the re-administration of 5-ASA on day four with one 4000 mg dose was performed as an unintentional rechallenge. At the same time, the diet of the patient was advanced to a reduced amount of nasogastric tube feeding combined with a small amount of solid food and liquid. Rechallenge resulted in recurrence of the epigastric pain after 8 hours and rapid elevation of pancreatic enzyme levels. The causal connection between the drug intake and AP was recognized, and drug-induced AP (DIAP) was diagnosed, the previous treatment was resumed and 5-ASA was permanently withdrawn. Repeat ultrasonography on day five was remarkable for a pancreas with slightly inhomogeneous, low echogenicity, consistent with acute inflammation (Fig. 2). On day seven, pain subsided, diet was advanced uneventfully, pancreatic enzyme levels dropped to nearly normal values, and the patient was discharged.

Both AP episodes were considered clinically mild, in spite of the marked increase in the leucocyte count, which we considered a consequence of the steroid therapy. The bedside index of severity in acute pancreatitis (BISAP) score at presentation was 1 [10].

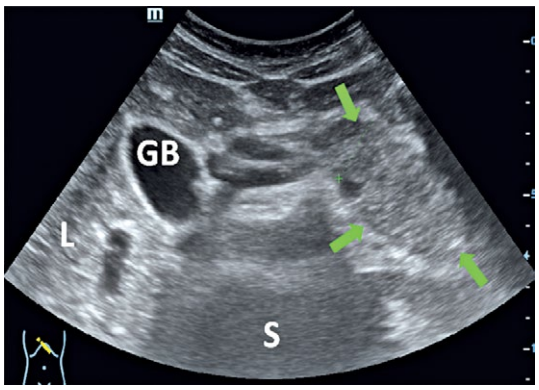

Fig. 2. Transabdominal ultrasonography one day after rechallenge with 5-ASA (06.08.2017): the pancreas (marked with arrows) is slightly inhomogeneous with low echogenicity, consistent with acute inflammation. L=liver, GB=gall bladder, S=spine.

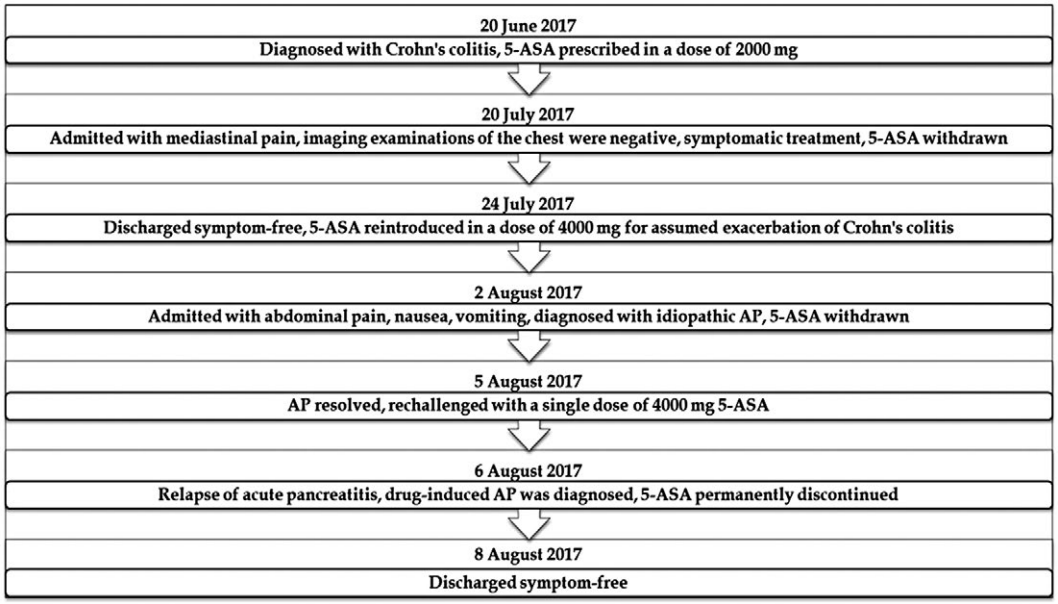

Fig. 1.Timeline of clinical course.

At the three-month follow-up, the patient had no recurrence of pancreatitis. Her Crohn's colitis symptoms are currently managed with budesonide and azathioprine. Magnetic resonance enterography four weeks after admission disclosed no involvement of the small bowel in Crohn's disease. Abdominal ultrasonography and magnetic resonance cholangiopancreatography (MRCP) performed five weeks after admission disclosed normal findings.

SYSTEMATIC REVIEW OF THE LITERATURE

We performed a systematic literature search on April 2017 on the databases PubMed, EMBASE and Web of Science with the search terms "5-ASA AND pancreatitis" with limitations of English language and human target, regardless of the date of publication (Fig. 3). Studies were included only if authors concluded that 5-ASA-derived medication was the most probable cause of the adverse drug reaction (ADR), meeting only one diagnostic criteria for AP according to the IAP/APA evidence-based guidelines, such as asymptomatic pancreatic enzyme level increase or abdominal pain. Thirty-five manuscripts, including 42 patients [1-5, 11-40] were identified applying this searching strategy (Table I). The ratio female/male was 24/19. The mean age was 26.88±11.1 years; 9 patients were pediatric cases (under 18 years of age). Most of the identified patients treated with 5-ASA derived drugs were suffering from ulcerative colitis (67.4%, n=29) and Crohn's disease (23.3%, n=10). One case of regional enteritis and one of unspecific colitis were found, and there was no data concerning the condition in two cases. Sulfasalazine was responsible in 35.7% (n=30) for the ADRs. 5-ASA in pH-dependent coating, in time-dependent coating and in otherwise non specified form caused ADRs in 22.6% (n=19), 8.3% (n=7) and 22.6% (n=19) of the identified cases. 5-ASA in enema form and Olsalazine were shown to cause ADRs in 11.9% (n=10) and 4.8% (n=4).

DISCUSSION

The most common etiologies for AP are gallstones, biliary sludge or microlithiasis, alcohol, smoking, hypertriglyceridemia, post-ERCP status, hypercalcemia, genetic mutations, infections or toxins, trauma, pancreas divisum and vascular disease [41, 42]. The rest of the episodes are usually termed idiopathic. Drug-induced AP is rare and challenging to identify because it has no clinical features to distinguish it from the more common etiologies of AP [43]. Moreover, because it is unethical to intentionally rechallenge with the offending drug due to the potentially life-threatening nature of pancreatitis, in most cases it remains a speculative diagnosis made by exclusion.

A classification of drugs reported to cause AP was made by Badalov et al. in 2007 [43], based on the published weight of evidence. Four classes of drugs were identified. Class Ia included drugs that previously had been described as positively rechallenged at least once, with all other etiologies ruled out. 5-ASA belonged to the class Ia category of drugs; nonetheless, cases with positive rechallenge and parallel exclusion of all other etiologies in the literature are still rare.

We analyzed the clinical course of 5-ASA-induced AP cases found on the systematic literature search. Hypersensitivity [1, 2, 11, 15, 37] and idiosyncrasy [1, 29] are usually thought to be involved in the pathogenic mechanism of 5-ASA-induced AP (according to 38.9% of the authors). In most of the identified cases, the reaction seemed not to be dose-dependent, however,

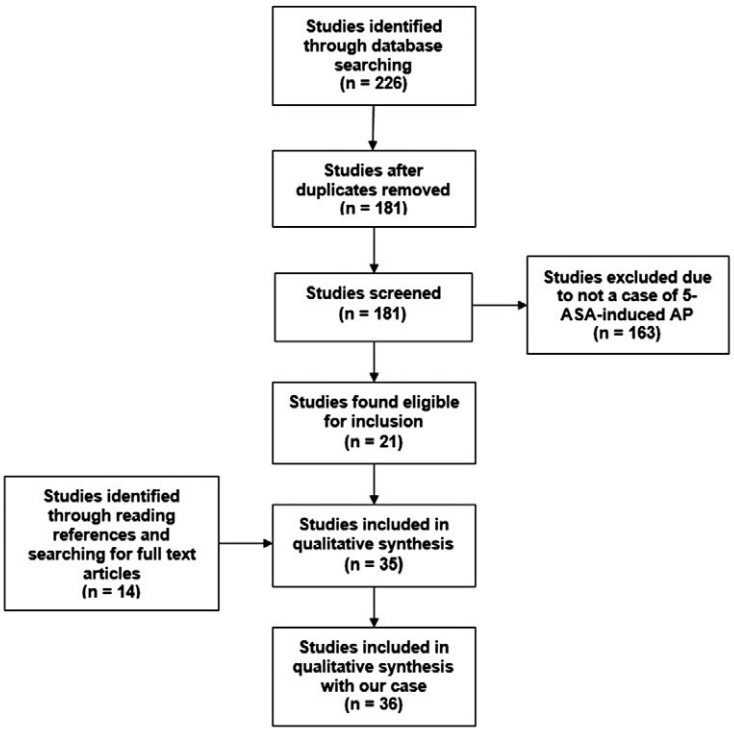

Fig. 3. Studies identified through systematic literature search

Table II. Possible etiological factors for acute pancreatitis

Possible etiologies	Patient history	Laboratory parameter or examination	Probable factor?
Biliary	No history	No gall stones. no biliary duct dilations on ultrasonography	no
Alcohol	Non-drinker	-	no
Smoking	Non-smoker	-	no
Hypertriglyceridemia	No history	0.62 mmol/L (ref: 0.00–1.70)	no
Post-ERCP	No ERCP done	-	no
Hypercalcemia	No history	2.28 mmol/L (ref: 2.15–2.55)	no
Genetic mutations	No family history	Negative for PRSS1	no
Infections, toxins	No history	No active mumps, rubeola, EBV, CMV, Varicella-zoster, HIV1 and 2, Hepatitis A, B, and C, HHV, Adenovirus	no
Trauma	No history	-	no
Pancreas divisum	No history	Excluded by MRCP	no
Vascular disease	No history	-	no
Extraintestinal manifestation of IBD	No history	Excluded by magnetic resonance enterography	no
Drug	Treatment for IBD	-	yes

the specific underlying mechanism remained a matter for speculation. We found one report of assumed dose-dependent toxicity [12]. The latency between intake of 5-ASA and onset of pancreatitis usually varied between a few days and a few months, however, DIAP can occur after long term treatment as well [4, 12, 21, 28, 35, 39]. The route of administration [4, 25, 29, 31, 39] (either oral or rectal) and use of coated formulations [1-3, 17] (time- or pH-dependent) did not appear to affect the risk of AP, and in most of the cases, there was a rapid recurrence if rechallenged [3, 12, 14, 15, 18]. 5-ASA induced AP was usually self-limited. In almost half (47.6%) of the identified cases, there was no data concerning the imaging of the pancreas, and in 13.1%, the imaging examinations showed normal findings. The severity of AP and length of hospitalization were mostly not described by the authors. In the cases which reported severity, AP was usually mild (73.7%) [2, 5, 11, 19, 22, 25, 28, 38], one moderately severe episode was found [31], and of the four severe cases reported [4, 20, 32], two were lethal; 60.5% of the identified patients (n=26) were rechallenged positively with one of the formulations of the 5-ASA. After discontinuation of the offending drug, symptoms usually disappeared quickly [3, 12, 14, 15, 18], as observed in our case as well.

Our patient had no fever, no skin rash or peripheral eosinophilia, which would be suggestive of an allergic reaction: the pathogenic mechanism was probably an idiosyncratic reaction [44], but hypersensitivity cannot be excluded. At presentation, medications were: 5-ASA for 41 days, metoprolol for three years, methylprednisolone for 13 days, pantoprazole for two weeks and potassium-chloride intermittently. We ruled out potassium chloride as the offending drug because it had never been suspected as a cause of AP. Metoprolol cannot be ruled out totally because it was previously noted to cause AP [45] in the literature. Our patient took metoprolol for three years without adverse events and during her entire hospitalization, including the time of pancreatic enzyme level normalization and symptomatic improvement. Few cases reported pantoprazole [46, 47] and methylprednisolone [48-54] induced AP, but in our patient, these drugs were continued throughout the hospital stay as well. Parallel to the rechallenge, our patient's diet was advanced, which could cause recurrence of AP. However, this is unlikely because repeated advancement two days later took place uneventfully.

Our patient's medical history strongly suggests that 5-ASA was the cause of her AP. We ruled out several other etiologies for AP (Table II). Our case therefore reached a score of 8, probable causality on the Naranjo adverse drug reaction probability scale [55].

CONCLUSION

Rechallenging with a drug which can be a possible cause of AP is ethically questionable and is usually not done because of the danger of recurrence of a potentially severe disease. Intentional rechallenge can be reasonable in rare cases if the drug is the only therapy of a life-threatening disease and re-administration is probably worth taking the risk. In our patient, the causal relationship between the drug intake and the first mild AP episode was not recognized first, and the patient was diagnosed with idiopathic AP; consequently, an unintentional positive rechallenge occurred, which has the biggest weight of evidence in assessing causality in the course of DIAP.

Conflicts of interest: No conflict to declare.

Authors' contributions: Á.M. conducted the acquisition of data and wrote the paper; Al.M. contributed to the acquisition and interpretation of data; P.H. made critical revisions to the manuscript on important intellectual content.

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Table I. Summary of 5-ASA-induced AP cases

Author		Patient			Drug			Acute pancreatitis			
Nr	**Name [reference]**	**Age**	**Sex**	**Condition**	**Active substance**	**Commercial name**	**Dose/day**	**Latency**	**Resolved**	**Rechallenge**	**Proposed pathomechanism**
1	Abdullah, AMA [1]	12	m	UC	Sulfasalazine	-	25 - 50 mg/kg	-	-	yes	Idiosyncratic or hypersensitivity
					Sulfasalazine	-	25 - 50 mg/kg	2 days	2 days		
					5-ASA e	-	2 g	-	-		
					5-ASA pH	-	1.2 g	3 days	2 days		
					5-ASA	-	1.2 g	1 day	-		
					5-ASA T	-	0.5 g	-	2 days		
2	Adachi, E [11]	24	f	UC	5-ASA	-	1.5 g – 2.25 g	9 days	7 days	no	Hypersensitivity
3	Al-Zayani, J [12]	23	f	UC	5-ASA pH	Asacol	1.2 g – 2.4 g	1 year	3 days	yes	Dose-related toxic
					Sulfasalazine	Azulfidine	3 g	9 days	-		
4	Anderson, JR [13]	39	f	UC	Sulfasalazine	Salazopyrin	3 g	-	-	yes	-
					Sulfasalazine	Salazopyrin	3 g	-	-		
					Sulfasalazine	Salazopyrin	3 g	-	-		
					Sulfasalazine	Salazopyrin	3 g	-	-		
					Sulfasalazine	Salazopyrin	3 g	-	-		
5	Arai, Y [2]	26	m	UC	5-ASA T	Pentasa	4 g	1 month	-	yes	Hypersensitivity
					Sulfasalazine	Salazosulfapyridine	-	Several weeks	-		
					5-ASA pH	Asacol	2.4 g	2 weeks	4 days		
6	Block, MB [14]	29	f	RE	Sulfasalazine	Salicylazosulfapyridine	4 g	2 weeks	-	yes	Unknown
					Sulfasalazine	Salicylazosulfapyridine	4 g	4 days	-		
					Sulfasalazine	Salicylazosulfapyridine	-	-	-		
					Sulfasalazine	Salicylazosulfapyridine	-	3 days	7 days		
7	Chiba, M [15]	33	m	UC	Sulfasalazine	Salazopyrin	2 g - 4 g	5 weeks	3 weeks	yes	Hypersensitivity
					Sulfasalazine	Salazopyrin	3 g	6 days	7 weeks		
					Sulfasalazine	Salazopyrin	1 mg - 100 mg	25 days	-		
8	Daniel, F	41	m	CD	5-ASA + 5-ASA e	-	4 g + 1 g	10 days	3 days	no	-

Author		Patient			Drug			Acute pancreatitis			
Nr	**Name [reference]**	**Age**	**Sex**	**Condition**	**Active substance**	**Commercial name**	**Dose/day**	**Latency**	**Resolved**	**Rechallenge**	**Proposed pathomechanism**
	[16]	29	f	UC	5-ASA + 5-ASA e	-	2 g + 1 g	3 days	Few days	no	
		36	f	UC	5-ASA	-	3 g	3 weeks	-	no	
9	Debongnie, JC [17]	29	f	CD	5-ASA	-	1.5 g	7 weeks	7 days	yes	-
					Sulfasalazine	-	3 g	2 weeks	-		
10	Deprez, P [18]	34	m	N/A	5-ASA pH	Claversal	1.5 g	2 weeks	3 days	yes	Unknown
					5-ASA pH	Claversal	-	12 hours	6 days		
11	Din, S [37]	31	f	CD	5-ASA T	Pentasa	-	4 weeks	7 days	no	Hypersensitivity
12	Erdkamp, F [19]	35	f	CD	5-ASA pH	Salofalk	1.5 g	6 days	5 days	yes	-
					5-ASA pH	Salofalk	1.5 g	2 days	3 days		
13	Eto, H [3]	25	f	UC	5-ASA pH	Asacol	-	2 weeks	-	yes	-
					5-ASA T	Pentasa	-	Several hours	-		
					5-ASA	-	-	7 hours	-		
14	Faintuch, J [20]	37	f	UC	Sulfasalazine	-	2 g - 1 g	6 weeks	-	no	Unknown
		14	f	CD	Sulfasalazine	-	1 g	5 days	-	no	
15	Fernandez, J [21]	24	f	UC	5-ASA	-	3 g	3 months	5 days	yes	Hypersensitivity
					5-ASA	-	3 g	1 day	5 days		
		34	m	UC	5-ASA	-	3 g	2 years	2 days	yes	
					5-ASA	-	-	12 hours	20 hours		
16	Fiorentini, MT [22]	30	m	UC	5-ASA pH	Asacol	0.4 g – 0.8 g	5 days	15 days	no	Hypersensitivity
		19	m	CD	5-ASA pH	Asacol	0.4 g – 1.6 g	22 days	-	yes	
					5-ASA pH	Asacol	0.4 g	14 days	-		
17	Garau, P [23]	12	m	UC	Olsalazine + 5-ASA e	Dipentum + Rowasa	1g + N/A	3 months	4 days	no	-
		13	f	UC	Sulfasalazine	-	1 g - 2 g	9 days	6 days	no	
		12	f	UC	Sulfasalazine	-	1.5 g - 1 g - 2 g	5 months	6 weeks	yes	
					Olsalazine	Dipentum	1 g	8 months	1 week		
18	Inoue, H [24]	40	m	UC	5-ASA	-	3 g	4 months	-	no	-
19	Isaacs, KL	19	f	UC	Sulfasalazine	-	3 g	3 weeks	-	yes	-

Author		Patient			Drug			Acute pancreatitis			
Nr	**Name [reference]**	**Age**	**Sex**	**Condition**	**Active substance**	**Commercial name**	**Dose/day**	**Latency**	**Resolved**	**Rechallenge**	**Proposed pathomechanism**
	[25]				5-ASA e	Rowasa	-	1 week	3 days		
20	Kutsenko, A [4]	63	f	UC	5-ASA pH 5-ASA pH+ 5-ASA e	Lialda Asacol + -	- -	2 years -	- -	yes	-
21	Manfredini, R [26]	29	f	AC	5-ASA	-	0.8 g	2 days	5 days	no	-
22	Niu, G [27]	28	f	UC	Sulfasalazine	-	6 g	70 days	-	no	-
23	Ouakaa-Kchaou, A [28]	33	m	UC	5-ASA	-	2 g - 4 g	18 months	-	no	-
24	Paerregaard, A [29]	7	f	UC	5-ASA T 5-ASA e	Pentasa Pentasa	1.5 g – 2.25 g 1 g	7 months 2 weeks	- 2 days	yes	Idiosyncratic or hypersensitivity
25	Paul, AC [5]	10	m	UC	5-ASA pH	Mesacol	0.8 g – 1.6 g	5 months	3 days	no	Hypersensitivity
26	Poldermans, D [30]	24	f	CD	Sulfasalazine Olsalazine Olsalazine	Salicylazosulfapyridine Dipentum Dipentum	4g 1.5 g 1.5 g	7 days 5 days 30 hours	- 7 days 2 days	yes	Hypersensitivity
27	Radke, M [31]	12	m	CD	Sulfasalazine 5-ASA pH 5-ASA e	- Salofalk Salofalk	2 g 1.5 g 4 g	2 weeks 1 week 1 week	- - 7 days	yes	-
28	Rubin, R [32]	37	m	UC	Sulfasalazine	Azulfidine	4 g	2 weeks	-	no	Hypersensitivity
29	Sachedina, B [33]	32	f	CD	5-ASA pH 5-ASA pH 5-ASA pH	Asacol Asacol Asacol	2.4 g 1.2 g 1.2 g	2 days 2 days 2 days	3 days 2 days 2 days	yes	Unknown
30	Suryapranata, H [34]	22	f	N/A	Sulfasalazine Sulfasalazine	- -	2 g -	- 1 day	12 days 2 days	yes	-
31	Tanigawara, Y [38]	43	m	UC	Sulfasalazine Sulfasalazine	Salazopirin Salazopirin	4 g 0.5 g	6 days 6 days	9 days 1 days	yes	-
32	Toubanakis, C [35]	19	m	UC	5-ASA 5-ASA	- -	2.4 g – 1.2 g 1.2 g	1 year 1 day	5 days 4 days	yes	Hypersensitivity

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33	Tran, K [36]	18	m	UC	5-ASA + 5-ASA e	-	4 g + 1 g	17 days	3 days	no	-
34	Uribarri-Gonzalez, L [39]	35	m	UC	5-ASA pH 5-ASA e	Claversal -	3 g -	2 years 2 weeks	- -	yes	-
35	Wada, S [40]	13	m	UC	5-ASA 5-ASA	- -	3 g -	- 1 day	- -	yes	Hypersensitivity
36	Our case	31	f	CD	5-ASA T 5-ASA T	Pentasa Pentasa	2 g - 4 g 4 g	6 weeks 8 hours	4 days 3 days	yes	Idiosyncratic

UC = ulcerative colitis, CD = Crohn's disease, RE = regional enteritis, AC = aspecific colitis, 5-ASA e = enema formulation, 5-ASA pH = pH dependent acrylic coated formulation, 5-ASA T = time dependent ethyl-cellulose coated formulation, Resolve of AP: time of symptomatic improvement and/or enzyme level normalization.