Lupus-like syndrome caused by 5-aminosalicylic acid in patients with inflammatory bowel disease

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BACKGROUND: Although 5-aminosalicylic acid (5-ASA) preparations used to treat inflammatory bowel disease are reported to have fewer side effects than sulphasalazine, increased clinical use of these compounds has resulted in increased reports of significant side effects.

OBJECTIVE: To report four patients with antinuclear antibody-positive migratory arthralgias and acute inflammation unrelated to the underlying inflammatory bowel disease, fulfilling the criteria of a drug-induced lupus-like syndrome.

SETTING: A university-affiliated teaching hospital.

INTERVENTION: Cessation of treatment with 5-ASA compounds.

RESULTS: The cases described constitute a drug-induced lupus-like syndrome. All patients improved rapidly after discontinuation of 5-ASA compounds.

CONCLUSIONS: Reversible lupus-like syndrome appears to be a rare but significant side effect of 5-ASA compounds. Patients treated with 5-ASA compounds who experience acute inflammatory symptoms or clinical deterioration not related to their gastrointestinal disease should be screened to rule out a lupus-like reaction.

Key Words: Aminosalicilic acids, Drug toxicity, Inflammatory bowel disease, Lupus-like syndrome

Syndrôme de pseudo-lupus provoqué par l'acide 5-aminosalicylique chez des patients atteints de maladie inflammatoire de l'intestin

DONNÉES DE BASE : Bien que selon les rapports, l'acide 5-aminosalicylique (5-AAS) provoque moins d'effets secondaires que la sulphasalazine, l'emploi clinique plus répandu de substances de ce type a entraîné des cas plus nombreux d'effets secondaires significatifs.

OBJECTIFS : Faire état de quatre cas d'arthralgie migratoire et d'inflammation aiguë positives à l'égard des anticorps antinucléaires, non liés à la maladie inflammatoire de l'intestin sous-jacente et répondant aux critères d'un syndrome de pseudo-lupus d'origine médicamenteuse.

CONTEXTE : Centre hospitalier universitaire.

INTERVENTION : Arrêt du traitement au 5-AAS.

RÉSULTATS : Les cas décrits sont des syndromes de pseudo-lupus d'origine médicamenteuse. L'état de tous les patients s'est rapidement amélioré après l'arrêt du traitement au 5-AAS.

CONCLUSIONS : Le syndrome de pseudo-lupus réversible semble un effet secondaire rare, mais important, des substances à base de 5-AAS. Les patients traités avec ces substances et qui manifestent des symptômes d'inflammation aiguë ou une détérioration clinique indépendante de leur maladie gastro-intestinale doivent subir des tests de dépistage pour que l'on puisse éliminer le diagnostic de syndrome de pseudo-lupus.

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Sulphasalazine is a proven effective treatment for ulcerative colitis (1-3). This drug, composed of a sulphapyridine and a 5-aminosalicylic acid (5-ASA) moiety, is not, however, without side effects. It has been appreciated for many years that sulphasalazine is capable of causing a systemic lupus erythematosus (SLE)-like disorder in patients suffering from inflammatory bowel disease (4-6). These adverse effects have been attributed to the sulphapyridine moiety, and thus the use of compounds containing only 5-ASA in patients demonstrating sulphasalazine-induced SLE has been recommended (7).

Adverse reactions to 5-ASA therapy include watery diarrhea, hypersensitivity reactions, perimyocarditis, pancreatitis and renal toxicity (8). Recently, other serious drug sensitivity reactions, previously believed to be related to the sulphapyridine moiety, have been reported with increasing frequency after treatment with 5-ASA, supporting the suspicion that 5-ASA compounds may not be free of lupus-like effects. Lim and Hine (9) reported a patient who developed fever, a vasculitic rash, arthritis, pericarditis and pericardial effusion after treatment with mesalazine. Welte and colleagues (10) reported 5-ASA-induced alveolitis associated with a generalized erythematous rash, and Hautekeete and colleagues (11) found evidence of hypersensitivity and hepatotoxicity after 5-ASA use. While these inflammatory reactions are clinically similar to the end-organ effects of drug-induced SLE, only two cases of 5-ASA-induced lupus-like syndrome have been reported. In 1992, Dent et al (12) reported a case occurring after mesalazine use (12), and in 1997, Gunnarson et al (13) reported a case occurring after the use of olsalazine. We report four cases of lupus-like syndrome occurring after the use of 5-ASA compounds.

CASE PRESENTATIONS

Case 1: A 26-year-old woman diagnosed with Crohn's disease at the age of 19 years had no previous rheumatic complaints. She was treated with 5-ASA (Asacol, Proctor & Gamble; 4 g daily) and prednisone (40 mg daily with a tapering dose). Colonoscopy revealed typical features of Crohn's colitis. When her disease improved after medical treatment and she was weaned from prednisone, she suffered repeated relapses requiring the reintroduction of prednisone. She had been started on maintenance oral 5-ASA at age 21 years. She noticed the onset of morning stiffness and arthralgias of the ankles, wrists and fingers, which improved promptly when she began taking prednisone (40 mg/day). Over the next two years, she continued to suffer recurrent episodes of arthralgia that remitted with increased steroid doses and worsened as the dose of steroids was tapered.

By November 1992, the patient developed elevated transaminase levels suggestive of a hepatic process – peak aspartate aminotransferase (AST) level 770 U/L and alanine aminotransferase (ALT) level 453 U/L; total and indirect bilirubin 24 and 13 mol/L, respectively; alkaline phosphatase (ALP) 156 U/L; gamma-glutamyltransferase 81 U/L (normal 5 to 25 U/L); 5'-nucleotidase 24 U/L (normal 2 to 10 U/L); and erythrocyte sedimentation rate (ESR) 35 mm/h. Other

TABLE 1
Serological findings in 5-aminosalicylic acid-treated patients

Test	Patient			
	1	2	3	4
ANA	1:320	1:320	1:640	1:320
Anti-DNA (<i>Crithidia</i> species)	+	+	+	+
Anti-DNA (Farr)	–	+	–	–
WBC/PMN ($\times 10^{-9}/L$)	9.3/7.6	8.5/6.2	29.7/17.5	8.3/5.7
Eosinophil ($\times 10^{-9}/L$)	0.01	0.01	6.2	0.01
ESR (mm/h)	35	25	48	26

ANA Antinuclear antibodies; ESR Erythrocyte sedimentation rate; PMN Polymorphonuclear leukocyte; WBC White blood cell count; + Positive; – Negative

hematological and serological markers of hepatitis were negative. The results of immunological studies were antinuclear antibody (ANA)-positive at 1:320 and anti-DNA (*Crithidia* species)-positive. Results of tests for anti-Sm, anti-RNP, anti-Ro and anti-La autoantibodies were negative (Table 1).

Diagnoses of drug-induced arthropathy and hepatitis were considered, and the 5-ASA was discontinued in December 1992. The arthritis resolved, and liver enzyme levels returned to normal. After all drugs were discontinued, including the steroids, her bowel habits remained normal. Biochemical tests indicated that her AST, ALT and ALP levels were normal by November 1993. Repeat ESR was 5 mm/h, and the anti-DNA (Farr) level was 2 U/L (normal less than 7 U/L). Her serology and transaminase levels were normal at her three-year follow-up examination.

Case 2: A 68-year-old man who presented with typical histological features of ulcerative colitis previously diagnosed with proctosigmoiditis was started on 5-ASA enemas (Salofalk, Axcan Pharma) and oral 5-ASA (Asacol; 4 g/day) in January 1992. After beginning the treatment, the patient began to complain of symptoms of polyarthralgias characterized by morning stiffness and pain in the shoulders, elbows and knees. His symptoms continued to progress throughout 1993. He had an ESR of 38 mm/h. Nonsteroidal anti-inflammatory drugs (NSAIDs) provided no relief, and prednisone and chloroquine only partially controlled his symptoms. An autoantibody screen revealed a positive ANA (1:320), a positive anti-DNA (*Crithidia* species) and an anti-DNA (Farr) of 12 U/L (normal less than 7 U/L), as well as a negative anti-Sm, anti-RNP, anti-Ro and anti-La (Table 1). His bowel disease remained in remission throughout the year, although the arthropathy continued to progress. After two years of therapy, the 5-ASA was discontinued; the rheumatic symptoms resolved completely within three weeks, with no exacerbation of the gastrointestinal disease. The patient's ANA levels and anti-DNA serology had reverted to normal at the follow-up examination eight months after 5-ASA discontinuation and remained normal at the two-year follow-up examination.

Case 3: A 23-year-old woman with a three-year history of left-sided ulcerative colitis was receiving 5-ASA (Salofalk) orally (2 g/day) and rectally (2 g nightly) when she began to experience multiple joint pains. The pains began with swollen index fingers, followed by pain in all proximal interphalangeal joints, and developed into a migratory nocturnal pain involving the knees, neck, back, shoulders and elbows. Results of the physical examination of the musculoskeletal system were unremarkable, and no effusions were noted; her gastrointestinal disease remained stable. The pain in her joints fully resolved with administration of prednisone (20 mg/day) for one week but recurred with gradual weaning of steroids.

Serological examination revealed a positive ANA of 1:640. Anti-DNA (*Crithidia* species) was positive at 9 U/L (normal less than 7 U/L); anti-DNA (Farr) level was 9 U/L (normal less than 7 U/L); and anti-Ro, anti-La, and anti-Sm autoantibody tests were all negative (Table 1). The eosinophil count was markedly elevated at $2.8 \times 10^9/L$ (normal $0.04 \times 10^9/L$ to $0.4 \times 10^9/L$ in a total leukocyte count of $9.5 \times 10^9/L$). The patient's symptoms resolved completely when the 5-ASA preparations were discontinued. Her ANA and anti-DNA antibody levels reverted to normal; she had a normal leukocyte profile at the one-year follow-up examination.

Case 4: A 47-year-old woman with previously negative autoimmune serology and a history of fibromyalgia was diagnosed with ileal Crohn's disease in 1994. She was initially successfully treated with 5-ASA 4 g (Pentasa, Hoechst Marion Roussel). Although her diarrhea cleared, she developed a rash on her forearms, upper arms and trunk, and arthralgia of her knees, ankles and wrists. Investigation revealed an elevated sedimentation rate, a positive ANA of 1:320, a positive lupus erythematosus cell preparation and a positive anticardiolipin antibody count of 51.5 U (Table 1). After six months on 5-ASA, the drug was discontinued. Her symptoms cleared within six weeks of cessation of therapy. She remained well one year later; the only abnormality has been a mildly elevated ANA level.

DISCUSSION

Drug-induced lupus was first associated with sulphadiazine (6,14,15). Since then, more than 50 other drugs have been implicated (14); procainamide and hydralazine are the most common agents (6,16,17). Various medications may induce seroreactivity by both dose-dependent and dose-independent mechanisms (14,18). Drug-induced lupus caused by sulphasalazine has been well described (17,18), and the following diagnostic criteria have been proposed (15,19).

- Absence of a history suggestive of idiopathic SLE before drug ingestion;
- Development of ANA and at least one clinical feature of lupus (eg, joint involvement, serositis, skin rashes) during sustained drug therapy; and

- Rapid improvement of clinical features after discontinuation of the drug.

This spectrum of 5-ASA-induced side effects, which includes arthropathy, biochemical evidence of hepatotoxins and ANA positivity, constitutes a lupus-like reaction that appears to be associated with 5-ASA and is reversible on discontinuation of the drug. Arthritis, the most commonly described extraintestinal manifestation of inflammatory bowel disease, occurs in up to 20% of patients with Crohn's disease (20,21) and ulcerative colitis (21,22). This seronegative arthritis usually consists of a migrating oligoarthritis involving fewer than four joints (20) that persists for weeks to months (22). In adults, arthritic attacks tend to coincide with flare-ups of bowel disease (20,21). The characteristic arthritis of drug-induced lupus is a nondeforming symmetrical polyarthritis that affects the small joints of the hands, then the wrists, elbows, shoulders, knees and ankles (6,15). Our patients exhibited ANA-positive arthropathies that worsened when the intestinal disease remitted and appeared to be partially responsive to steroid therapy. Musculoskeletal complaints caused by drug-induced lupus are usually controlled with NSAIDs or short courses of steroids (15). However in these cases the patients did not respond to NSAIDs.

Only a minority of patients with a positive ANA develop a clinical disease in response to medication (17). It is not necessary to discontinue a medication solely on the basis of an ANA seroconversion (6,14,15). However, when clinical symptoms or end-organ effects are noted, suspect medication should be withdrawn (6,14). Most symptoms of drug-induced lupus are self-limiting when the offending drug is discontinued and conservative management instituted (6,15).

Patient 3 had marked eosinophilia. Mild increases in the number of circulating eosinophils, up to but not exceeding $0.8 \times 10^9/L$, have been described in cases of ulcerative colitis (23,24). Anecdotal evidence of pronounced eosinophilia coincident with clinical relapse has been reported in patients with ulcerative colitis. Regardless, the rapid improvement that occurred when the 5-ASA treatment was discontinued supports our belief that the patients' symptoms were secondary to the 5-ASA.

The lupus-like syndrome induced by 5-ASA appears to be a rare, potentially serious, yet easily treatable complication of 5-ASA treatment. The syndrome appears to be reversible when the 5-ASA treatment is discontinued. We believe that the four cases presented are examples of a drug-induced lupus-like reaction to 5-ASA compounds. Ethical considerations did not allow a rechallenge, which would have further confirmed this relationship. Most arthropathies in patients with inflammatory bowel disease are extraintestinal manifestations of the underlying disease. In cases in which patients exhibit inflammatory symptoms such as arthropathies or hepatitis after 5-ASA therapy, the possibility of an adverse idiosyncratic reaction to 5-ASA compounds should be considered. Serological studies to screen for abnormal ANA in these settings may be warranted. A trial of discontinuation of

the 5-ASA compound may result in cessation of the symptoms and indicate an adverse reaction to 5-ASA.

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