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SHORT REPORT

Thiopurines, a previously unrecognised cause for fatigue in patients with inflammatory bowel disease☆

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Abstract

Background: Active inflammatory bowel disease, anaemia, iron deficiency and depression, alone or in combination, are known contributing factors of fatigue in inflammatory bowel disease. However, in some patients, fatigue cannot be attributed to known causes. Thiopurines are not a recognized cause.
AIM: To describe the clinical scenario of a series of patients where thiopurines were the likely cause of fatigue.
Method: The clinical scenario of 5 patients was examined with specific reference to the temporal association of thiopurine therapy with fatigue, the effect of its withdrawal and rechallenge, and drug specificity.
Results: The onset of severe fatigue was related to the introduction of azathioprine or 6-mercaptopurine, rapid relief was experienced on its withdrawal in all patients, and fatigue rapidly occurred on rechallenge. The speed of onset was rapid in two patients and in the context of gradual withdrawal of moderate steroid dose, but recurred rapidly on rechallenge when not on steroids.
Conclusions: Marked fatigue is a previously unrecognized adverse effect of thiopurines. It does not appear to be drug-specific. Its onset might be masked by concurrent steroid therapy.

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1. Introduction

Fatigue is a common symptom in patients with inflammatory bowel disease (IBD) and often relates to active disease, anaemia, iron deficiency and depression, alone or in combination. However, in some patients, fatigue cannot be attributed to a known cause. This symptom has not previously been ascribed to treatment with thiopurines. We describe here the clinical scenario of five patients where thiopurines were the likely cause.

2. Case reports

2.1. Patient 1

A 44 year old female social welfare worker was referred with steroid-dependent distal ulcerative colitis in early 2007. Azathioprine was initiated in late 2007 at a dose of 25 mg/day increasing by 25 mg/day each fortnight. At 75 mg/day and prednisolone 40 mg/day, her bowel habit returned to normal and C-reactive protein (CRP) had normalized. Iron studies were normal and there was no suggestion of depression. Severe fatigue and lethargy occurred at day 10 of azathioprine initiation such that she was bed-ridden. Prompt resolution of fatigue occurred within two weeks of stopping azathioprine. She has declined re-challenge with azathioprine or 6-mercaptopurine (6-MP).

2.2. Patient 2

A 29 year old woman was diagnosed with terminal ileal Crohn's disease in 2002. After a prolonged course of prednisolone and an episode of steroid-induced psychosis, azathioprine was initiated at 200 mg/day. The dose was reduced to 150 mg/day because of neutropenia. She noted a gradual onset of fatigue with decreased energy level and poor concentration span affecting her work a few weeks after its initiation. These symptoms resolved one week after the cessation of azathioprine. In 2004, she had an ileocaecectomy for small bowel obstruction in the context of no active medical therapy. Post-operatively, she was restarted on azathioprine 150 mg/day. The level of 6-methyl-mercaptopurine was in the non-toxic range and that of 6-thioguanine nucleotide was therapeutic, but fatigue returned. It did not improve on dose reduction, but resolved rapidly upon cessation of azathioprine. During this time, her inflammatory markers were normal and there was no evidence of iron deficiency or anaemia. She was not depressed. She was subsequently challenged with 6-MP and a similar fatigue profile returned. This resolved with cessation of the drug.

2.3. Patient 3

A 39 year old male smoker was diagnosed with stricturing ileocolonic Crohn's disease at the age of 23. After frequent episodes of subacute small bowel obstruction responding to oral corticosteroids, azathioprine was initiated at 50 mg/day and the dose was increased to 150 mg/day over six weeks accompanied by weaning of prednisolone. During this time, the patient felt tired and lethargic which affected his ability to work as a courier. His inflammatory markers were normal but he was iron deficient. After a total dose iron infusion, his energy level improved only transiently. The fatigue did not respond to azathioprine dose reduction, but resolved within two weeks of its cessation. He was then commenced on 6-MP 50 mg/day and the dose was incrementally increased to 125 mg/day over 6 weeks. Fatigue recurred this time with myalgia. The 6-methyl-mercaptopurine level at the time was in the non-toxic range and the 6-thioguanine nucleotide level was sub-therapeutic. His bowel symptoms were stable and he was not iron deficient or anaemic. Three weeks after stopping 6-MP, his fatigue resolved.

2.4. Patient 4

A 63 year old storeman with distal ulcerative colitis was started on azathioprine 25 mg/day after requiring multiple courses of oral prednisolone for active disease. When the dose of azathioprine was increased to 50 mg/day, he experienced generalized lethargy. Concurrent medication at the time was a high dose of 5-aminosalicylic acid (5-ASA). Fatigue resolved one week after stopping azathioprine. Six months later, 6-MP 25 mg/day was introduced whilst on a stable dose of 5-ASA. He had no bowel symptoms and the colon was endoscopically normal. When 6-MP was increased to 75 mg/day, he experienced a gradual onset of fatigue, which was severe enough to prompt his early retirement from work. His stools were formed, he was not anaemic or iron deficient, and his inflammatory markers were normal. Thiopurine metabolite levels at the time were within the therapeutic and non-toxic ranges. There were no features to suggest a depressive illness. With worsening of fatigue over the next two months, 6-MP was discontinued and the fatigue resolved within a week.

2.5. Patient 5

A 74 year old ex-smoker with chronic airflow limitation and osteoporosis was diagnosed with distal ulcerative colitis in 2002. The disease was steroid responsive but had low grade chronic activity and multiple exacerbations. A further exacerbation of colitis in 2008 responded incompletely to increased topical therapy (5-ASA and corticosteroids). Mildly active disease involving the rectum and sigmoid colon was found at colonoscopy and confirmed histologically. He was commenced on oral prednisolone and his bowel habit rapidly normalized. Azathioprine 50 mg/day was introduced whilst the dose of prednisolone was being tapered. Iron studies were normal, he was not anaemic and he had no features to suggest depression. Azathioprine was increased by 50 mg/day each fortnight, but, at 150 mg/day, he noted an acute onset of extreme lethargy and tiredness, accompanied by a transient development of rash over his extremities. He was taking 12.5 mg/day prednisolone at that time. The full blood examination was unremarkable. His energy levels improved gradually over the next week with cessation of azathioprine. Rechallenge with 6-MP was refused by the patient.

3. Discussion

Fatigue is a pervasive symptom which results from complex biological, psychosocial and behavioural processes. However, fatigue has received only limited attention in the setting of IBD. Fatigue is well recognised in association with active inflammatory disease and is likely to be a direct effect of systemic exposure to pro-inflammatory cytokines such as tumour necrosis factor alpha and interleukin-6, since infusing these induces fatigue,[1] circulating levels correlate with clinical fatigue,[2] and treatment with infliximab leads to significant improvement in fatigue.[3] However, even in remission, abnormal fatigue may be present in 41% of patients and the fatigue scores were in line with those in patients with cancer before and after radiotherapy.[4] There are multiple factors other than inflammation that might contribute to fatigue and these include anaemia,[5] iron deficiency without anaemia,[6] psychological comorbidity, such as anxiety, depression and sleep disturbance.[7,8]

Drugs themselves have the potential to directly contribute to fatigue. Thiopurines are commonly used in patients with IBD, but fatigue has not been specifically recognised as a potential adverse effect. Evidence that thiopurine use is the likely cause of fatigue in the current series of patients is outlined in Table 1. Alternative known causes of fatigue, including active inflammatory disease, depression, anaemia and iron deficiency were not present. Since there were few clues that adrenal insufficiency might be present, other than fatigue and a history of corticosteroid therapy, specific investigation of the hypothalamic-pituitary-adrenal axis was not undertaken in any patient. A previous study of a large cohort of patients with fatigue and prolonged corticosteroid use could find no evidence of adrenal insufficiency indicating that this is not a common cause of fatigue.[4] In the current case series, the onset of fatigue was closely related temporally to the initiation of thiopurines, withdrawal of the drug led to rapid reduction in the fatigue in all, and rechallenge in three patients with azathioprine and/or 6MP led to reappearance of fatigue that responded to subsequent cessation of therapy. Fatigue did not appear to be specific to azathioprine as it was also observed with 6MP. There was an apparent dose-related effect in some of the case studies where only small, presumably sub-therapeutic doses, were tolerated. The onset was slow and gradual in some patients who were also taking corticosteroids and the likelihood that such therapy masked thiopurine-induced fatigue seems reasonable.

How thiopurines might cause fatigue is unknown. The myalgia/arthralgia syndrome and profound muscular weakness are believed to be immune-mediated reactions.[9,10] The symptoms recur within hours of rechallenge with azathioprine but may not when challenged with 6MP.[9,10] Alternatively, inosine triphosphate pyrophosphatase (ITPase) deficiency with resultant accumulation of 6-thio-ITP has been associated with the occurrence of myalgia and flu-like symptoms.[11] However, the association was not found in another study.[12] While one patient in the present series had myalgia, the presentation and clinical syndrome was different to the myalgia/arthralgia syndrome, rechallenge led to slow onset of fatigue, and 6MP had the same effect. Thiopurine metabolite profiling was only performed in three patients and this did not show a pattern that might be amenable to concurrent allopurinol therapy.[13]

The frequency of fatigue is likely to be very uncommon since the current series of patients is derived from a large IBD Clinic in a tertiary referral centre. Nevertheless, fatigue is common in patients with IBD in remission and recognizing a correctable cause is clinically desirable since such symptoms can markedly impair a patient's quality of life and can lead to unnecessary investigation. Importantly, thiopurine-induced fatigue resolves rapidly; a trial of drug cessation for a few of weeks where fatigue is troublesome and poorly explained is, therefore, a reasonable and practical action that is unlikely to be detrimental to control of the underlying disease process. Unfortunately, the use of an alternative thiopurine was not successful in the current patient series and such an observation suggests that an alternative immune modulating drug class be used when fatigue appears causally related to azathioprine or 6MP.

Table 1 Patient details and the relationship between thiopurine use and fatigue.

Age, sex		29 years, female	44 years, female	39 years, male	63 years, male	74 years, male
Disease characteristics	*Disease*	Crohn's disease	Ulcerative colitis	Crohn's disease	Ulcerative colitis	Ulcerative colitis
	Distribution	Terminal ileal	Distal	Ileo-colonic	Distal	Distal
Alternative cause for fatigue	*Anaemia*	No	No	No	No	No
	Iron deficiency	No	No	No	No	No
	Active disease (evidence)	No (post-resection)	No (normalized CRP)	No (normalized CRP)	No (endoscopy)	Mild left sided UC (endoscopy)
	Depression	No	No	No	No	No
Temporal relationship with thiopurine	*Challenge*	Rapid onset	Rapid onset (with steroid withdrawal)	Gradual (with steroid withdrawal)	Gradual onset at therapeutic dose	Rapid onset (with dose escalation/ steroid withdrawal)
	Withdrawal	Rapid relief	Rapid relief	Rapid relief	Rapid relief	Rapid relief
	Rechallenge	AZA, 6MP - Recurred	Refused	6MP - Recurred	6MP-Recurred	Refused

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