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Original Article

Azathioprine Hypersensitivity Syndrome in a Cohort of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Patients

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What is already known about the topic? Azathioprine hypersensitivity syndrome is a rare adverse effect of azathioprine therapy associated with fever, nausea, arthralgia, and cutaneous eruptions. It should be separated from other drug-related side effects, such as hepatotoxicity and leukocytopenia.

What does this article add to our knowledge? Although earlier studies were mostly case reports/series or literature overviews, this study gives more accurate estimations of the incidence of azathioprine hypersensitivity syndrome and its characteristics within an observational cohort. This helps in its identification.

How does this study impact current management guidelines? Its frequency (9%) warrants more awareness of azathioprine hypersensitivity as a cause of systemic inflammation and skin eruptions. It should be an important differential diagnosis besides infection or relapse for clinical deterioration after starting azathioprine.

BACKGROUND: Azathioprine hypersensitivity syndrome is a rare complication of azathioprine therapy. Its symptoms resemble infection or relapse of inflammatory disease, hindering correct diagnosis. Current literature is limited to sporadic case reports and reviews.

OBJECTIVE: To estimate the incidence of azathioprine hypersensitivity syndrome and describe its characteristics in the context of an observational cohort of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Also, to facilitate early recognition and awareness among clinicians.

METHODS: Within a cohort of 290 patients with ANCA-associated vasculitis receiving azathioprine maintenance therapy, frequency of azathioprine hypersensitivity was described and characteristics were compared between hypersensitive and non-hypersensitive patients. Clinical picture, laboratory abnormalities, and concurrent medication of patients with azathioprine hypersensitivity were described.

RESULTS: Of 290 patients, 25 (9%) experienced azathioprine hypersensitivity after a median of 14 (interquartile range [IQR] 12-18) days. Frequent symptoms were fever (100%), malaise (60%), arthralgia (36%), and rash (32%). All patients used prednisolone (median 10 mg/day, IQR 9.4-16.3 mg/day) at the time of the hypersensitivity reaction. Most patients had a rise in C-reactive protein (CRP), leukocyte counts, and neutrophil counts, but no eosinophilia. Thiopurine S-methyltransferase (TPMT) activity was significantly lower in hypersensitive patients (median 74.4 [IQR 58.0-80.1] nmol/gHb/L) compared with controls (median 81.4 [71.9-90.5] nmol/gHb/L), $P = .01$. Hypersensitive patients had a higher risk of relapse (hazard ratio 2.2, 95% confidence interval 1.2-4.2; $P = .01$).

CONCLUSIONS: Azathioprine hypersensitivity syndrome is strikingly common in ANCA-associated vasculitis, might be associated with reduced TPMT activity, is accompanied by an increase in neutrophil counts, and may occur even during concomitant prednisolone therapy. Proper recognition may prevent unnecessary hospital procedures and damage to the patient. **(J Allergy Clin Immunol Pract 2019;7:1004-9)**

Key words: *Azathioprine; Thiopurines; Drug hypersensitivity; ANCA; Vasculitis; Granulomatosis with polyangiitis; Microscopic polyangiitis; Eosinophilic granulomatosis with polyangiitis; Thiopurine methyltransferase; Cohort study*

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Abbreviations used
6-MP- 6-Mercaptopurine
6-TGN- 6-Thioguanine nucleotides
ANCA- Antineutrophil cytoplasmic antibody
CI- Confidence interval
EGPA- Eosinophilic granulomatosis with polyangiitis
GPA- Granulomatosis with polyangiitis
IBD- Inflammatory bowel disease
IQR- Interquartile range
MS- Multiple sclerosis
TPMT- Thiopurine S-methyltransferase

Azathioprine is widely used for the treatment of inflammatory conditions including inflammatory bowel disease (IBD) and multiple sclerosis (MS). In antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), a group of autoimmune diseases comprising granulomatosis with polyangiitis (GPA), microscopic polyangiitis, nephritic crescentic glomerulonephritis, and eosinophilic granulomatosis with polyangiitis (EGPA),[1] azathioprine is used as maintenance therapy after remission induction, usually with cyclophosphamide or rituximab.[2]

A relatively uncommon adverse effect of azathioprine is a hypersensitivity syndrome characterized by systemic symptoms such as fever, arthralgia, abdominal pain, and nausea, with or without cutaneous symptoms.[3] Because of the clinical picture of the hypersensitivity reaction and accompanying laboratory abnormalities, it can be mistaken for an infection or relapse of vasculitis activity.[4] Although usually self-limiting on termination of azathioprine therapy, the azathioprine hypersensitivity syndrome can be life-threatening with shock and acute renal insufficiency as possible features.[5,6]

The pathogenesis of azathioprine hypersensitivity syndrome has not been fully elucidated. A type III (immune complex—mediated) and type IV (T-cell—mediated) reaction are possible underlying types of hypersensitivity.[3,7] As neutrophilia is frequently seen in patients with azathioprine hypersensitivity, neutrophils might also play a role in the pathogenesis.[7]

Azathioprine is a prodrug. It is first enzymatically converted into 6-mercaptopurine (6-MP), which is further converted through 1 of 3 competing pathways. Conversion of 6-MP by hypoxanthine phosphoribosyltransferase results in 6-thioguanine nucleotides (6-TGN), the active metabolites responsible for the cytotoxicity of azathioprine. By contrast, conversion by xanthine oxidase results in formation of inactive thiouric acid, whereas conversion by thiopurine S-methyltransferase (TPMT) results in formation of inactive 6-methylmercaptopurine.[8]

The gene encoding TPMT is localized on chromosome 6.[8] Several single nucleotide polymorphisms have been described for this gene. The most common variants in Caucasians, besides wild-type (TPMT*1), are TPMT*2 (C>G at rs1800462), TPMT*3A (C>T at rs1800460 and T>C at rs1142345), TPMT*3B (C>T at rs1800460), and TPMT*3C (T>C at rs1142345). All of these are nonfunctional variants causing reduced TPMT activity.[9] This indirectly results in increased levels of 6-TGN and, therefore, increased myelotoxicity.[8,10] In previously published cases of azathioprine hypersensitivity, patients had a normal TPMT genotype and activity. Therefore, TPMT is not considered to be related to the occurrence of azathioprine hypersensitivity.[3]

The treatment of azathioprine hypersensitivity syndrome is generally not required, as symptoms usually resolve within a few days after discontinuation of azathioprine.[3,7] Switching from azathioprine to 6-MP and vice versa was successful in a minority of cases.[3,11] Also, several cases of successful desensitization have been reported.[11] In case of AAV, most patients switch to other maintenance therapy, usually mycophenolate mofetil, methotrexate, or rituximab, in accordance with treatment guidelines.[2]

So far, studies on azathioprine hypersensitivity were mostly case reports, case series, or literature overviews of such studies. This does not allow for an adequate estimation of the incidence and distribution of symptoms of the azathioprine hypersensitivity syndrome. This study describes the incidence of azathioprine hypersensitivity, distribution of symptoms, associated laboratory abnormalities, and concomitant medication use within an observational cohort of patients with ANCA-associated vasculitis treated with azathioprine maintenance therapy according to a local AAV treatment protocol.

METHODS

Participants

The study is part of a single-center observational cohort study investigating potential biomarkers related to disease outcomes in patients with ANCA-associated vasculitis, diagnosed and treated in the Vasculitis Expertise Center of the University Medical Center Groningen between 1972 and 2017. Recruitment for the present study took place between July 2010 and April 2017. During this period, 12 of 359 patients approached refused participation in the observational cohort. Of the remaining 347 patients, 57 were excluded because they never used azathioprine during follow-up. The remaining 290 patients with ANCA-associated vasculitis were included for analysis. All patients provided written informed consent for participation in the cohort study. In addition, 1 patient provided written informed consent to publish his clinical photographs, made at the time of azathioprine hypersensitivity, in a scientific journal. The study was approved by the local medical ethical committee of the University Medical Center Groningen (METc 2010/057) and was conducted according to the principles outlined in the Declaration of Helsinki (Fortaleza, Brazil, October 2013).

Patients with documented fever (temperature >38°C) and/or elevated C-reactive protein (CRP >5 mg/L) and/or skin manifestations and/or reoccurrence of the same symptoms within a day after rechallenge, attributed to azathioprine and resolving within a week after stopping the drug, were labeled as cases. All other patients were labeled as controls. All patients were approached and asked consent by their physician for a rechallenge with a small dose (25 mg) of azathioprine. A positive rechallenge of azathioprine hypersensitivity was defined as reoccurrence of fever and/or other symptoms attributed to azathioprine hypersensitivity after rechallenge with azathioprine, which improved within days after discontinuation of azathioprine.

Data collection

All data were retrieved from the patients' medical records. Follow-up data were collected until May 2018. Demographic and disease characteristics as well as any relapses within 60 months after start of therapy, or until the last visit if follow-up was shorter than 60 months, were collected for all patients. A relapse of vasculitis was defined as any disease activity requiring new immunosuppressive therapy or intensification of current treatment, in accordance with European League Against Rheumatism (EULAR) recommendations.[12] For cases with azathioprine hypersensitivity, if present,

symptoms of azathioprine hypersensitivity, laboratory values before start of azathioprine and during azathioprine hypersensitivity, as well as concurrent medication use were collected.

Statistics

Statistical analysis was performed using SPSS Statistics 23 (IBM Corporation, Armonk, NY). A 2-sided P value $<.05$ was considered statistically significant. Missing data were handled using pairwise deletion. Continuous variables were described as median (interquartile range [IQR]); categorical variables were described as n (%). A 95% confidence interval (CI) around the proportion of patients with azathioprine hypersensitivity was calculated using the Wilson procedure with continuity correction.[13] Demographic and disease characteristics were compared between cases and controls using the Mann-Whitney U test for continuous variables and the Fisher exact test for categorical variables. Subsequently, time intervals, symptoms, and laboratory findings were described for cases of febrile azathioprine hypersensitivity. Finally, the risk of relapse up to 5 years after the start of induction therapy was compared between cases and controls using Cox proportional hazards analysis. The proportionality assumption of Cox regression was tested using scaled Schoenfeld residuals (R version 3.4.2). After univariable survival analysis, multivariable Cox regression was performed with correction for TPMT activity and ANCA specificity (proteinase 3 vs myeloperoxidase/other/negative) because of their known relation with relapse/efficacy of azathioprine therapy and the baseline differences observed in this study.

RESULTS

Patients

Of the 290 patients included, 25 (8.6% [95% CI 5.8% to 12.6%]) had a febrile hypersensitivity reaction, of whom 16 were confirmed through rechallenge; 9 patients refused rechallenge. Several differences were found between patients with and without azathioprine hypersensitivity. First, patients with azathioprine hypersensitivity had a significantly lower TPMT activity (median 74.4 [IQR 58.0-80.1] nmol/gHb/hour) compared with controls (median 81.4 [IQR 71.9-90.5] nmol/gHb/hour; $P = .01$). This translates into a higher frequency of patients with reduced ($\leq$52 nmol/gHb/hour) TPMT activity (5 [20%]) in cases compared with controls (19 [7%]; $P = .05$). Second, they had a higher frequency of variant TPMT carriers (5 [20%]) compared with controls (22 [9%]; $P = .05$). Finally, there was a trend toward a lower frequency of patients classified as GPA in the hypersensitive group (13 [52%]) compared with the control group (198 [75%]; $P = .06$). Baseline results are summarized in Table I.

Symptoms of azathioprine hypersensitivity

Besides fever (diagnostic criterion in this study), the most frequent symptoms noted in the group of 25 hypersensitive patients were malaise, chills, arthralgia, myalgia, skin involvement, and gastrointestinal complaints (see Table II). Four patients (16%) experienced acute kidney injury and 1 patient (4%) experienced circulatory shock. Median interval between the start of azathioprine and complaints was 14 days (IQR 12-18, range 7-37 days). All 16 rechallenged patients had a recurrence of symptoms within hours. The symptoms of patients with rechallenge confirmed (definite) hypersensitivity were similar in type and frequency to those of patients without rechallenge. All symptoms including frequencies are summarized in Table II. An example of skin involvement is shown in Figure 1.

Laboratory values of hypersensitive patients

In total, 12 patients had laboratory evaluation at the time of azathioprine hypersensitivity. Most patients had a rise in CRP and neutrophil counts compared with the values before starting azathioprine (see Table III). During the hypersensitivity reaction, the most frequent laboratory abnormalities were elevated CRP, present in all 12 patients, and neutrophilia, present in 7 of 9 measured patients (78%). No eosinophilia was observed.

Concurrent medication

Median azathioprine dose of hypersensitive patients was 100 mg/day (IQR 100-150 mg/day). All patients used prednisolone (median 10 mg/day, IQR 9.4-16.3 mg/day) at the time of the hypersensitivity reaction.

Clinical course after azathioprine hypersensitivity

Of all 25 hypersensitive patients, 13 (52%) switched to mycophenolate mofetil, 7 (28%) to cyclophosphamide, 2 (8%) to methotrexate, and 3 (12%) received no therapy after azathioprine hypersensitivity. Relapse data were available for 24 of 25 hypersensitive patients and 257 of 265 nonhypersensitive controls. In total, 12 (50%) hypersensitive cases and 104 (40%) controls experienced a relapse of vasculitis within 5 years. In univariable Cox regression, azathioprine hypersensitivity was not associated with risk of relapse (hazard ratio [HR] 1.4, 95% CI 0.8-2.6; $P = .25$). In multivariable Cox regression, after correction for ANCA specificity and TPMT activity, azathioprine hypersensitivity was a statistically significant risk factor of relapse (HR 1.9, 95% CI 1.0-3.6; $P = .04$).

DISCUSSION

In this description of azathioprine hypersensitivity cases within our single-center cohort of 347 patients with ANCA-associated vasculitis, there were several unexpected findings.

First, febrile azathioprine hypersensitivity occurred in 9% (95% CI 6% to 13%) of azathioprine users, which is more frequent than the 2% (95% CI 1% to 4%) frequently mentioned based on a cohort study of patients with IBD using 6-MP.[11] On the other hand, similar frequencies of febrile azathioprine hypersensitivity were found in patients with MS (10% [95% CI 4% to 23%]) and IBD (6% [95% CI 3% to 11%]) using azathioprine.[14,15] Indeed, some previously reported patients have successfully switched from 6-MP to azathioprine,[11] or vice versa,[16,17] indicating that the imidazole group of azathioprine is an additional epitope capable of inducing azathioprine hypersensitivity, besides epitopes from 6-MP and/or its metabolites. This might explain a higher frequency of hypersensitivity in azathioprine-treated populations compared with 6-MP-treated populations. The high frequency of azathioprine hypersensitivity in this population is given more relevance by our finding that febrile azathioprine hypersensitivity is an independent risk factor of relapse, most likely due to the necessity of a switch to less effective maintenance therapy.[2] The interval between the start of azathioprine and onset of symptoms (median 14 days), and the most frequently occurring symptoms (fever, malaise, arthralgia, skin eruption) were similar to those described previously.[3]

Second, hypersensitive patients had a significantly lower TPMT activity compared with controls, with 20% of hypersensitive patients having reduced TPMT activity ($\leq$52 nmol/gHb/hour) compared with 7% of controls. Earlier studies did not

TABLE I. Patient characteristics

Characteristic	All (n = 290)	Hypersensitive (n = 25)	Control (n = 265)	*P* value
Age at AAV diagnosis (y)	54 (42-63)	56 (45-66)	53 (41-63)	.22
Duration of follow-up (m)	48 (27-60)	49 (28-60)	44 (16-60)	.31
Female, n (%)	140 (48)	8 (32)	132 (50)	.10
Diagnosis				.06
GPA	211 (72.8)	13 (52)	198 (75)	
MPA	42 (14.5)	6 (24)	36 (14)	
NCGN	13 (4.5)	2 (8)	11 (4)	
EGPA	24 (8.3)	4 (16)	20 (8)	
ANCA specificity				.22
PR3	200 (69.0)	13 (52)	187 (71)	
MPO	62 (21.4)	8 (32)	54 (20)	
Other	4 (1.3)	0 (0)	4 (1)	
Negative	24 (8.3)	4 (16)	20 (8)	
TPMT genotype	N = 280/290	N = 25/25	N = 255/265	.05*
*1/*1	253 (90)	20 (80)	233 (91)	
*1/*3A	22 (8)	3 (12)	19 (8)	
*1/*3C	5 (2)	2 (8)	3 (1)	
TPMT activity (nmol/gHb/h) (n = 283/290)	80.4 (70.2-90.4)	74.4 (58.0-80.1)	81.4 (71.9-90.5)	.01*
Low TPMT activity (≤52.0 nmol/gHb/h)	N = 283/290 24 (9%)	N = 25/25 5 (20%)	N = 258/265 19 (7%)	.05*

Baseline characteristics for all included patients, split out for patients with azathioprine hypersensitivity, and azathioprine-tolerant patients. Data described as n (%) or median (IQR).

AAV, Antineutrophil cytoplasmic antibody-associated vasculitis; *ANCA*, antineutrophil cytoplasmic antibody; *EGPA*, eosinophilic granulomatosis with polyangiitis; *GPA*, granulomatosis with polyangiitis; *IQR*, interquartile range; *MPA*, microscopic polyangiitis; *MPO*, myeloperoxidase; *NCGN*, nephritic crescentic glomerulonephritis; *PR3*, proteinase 3; *TPMT*, thiopurine S-methyltransferase.

*$P < .05$.

TABLE II. Symptoms of azathioprine hypersensitivity syndrome

Symptom	All hypersensitive (n = 25)	Rechallenge confirmed (n = 16)
Patient reported		
Fever*	25 (100)	16 (100)
Malaise	15 (60)	10 (63)
Arthralgia, myalgia	9 (36)	6 (38)
Chills	5 (20)	5 (31)
Gastrointestinal (pain, nausea, vomiting)	5 (20)	4 (25)
Objective		
Skin involvement	8 (32)	4 (25)
Acute kidney injury	4 (16)	2 (13)
Hypotension/circulatory shock	1 (4)	1 (6)
Hepatotoxicity	0 (0)	0 (0)

Overview of frequency of azathioprine hypersensitivity symptoms in the cohort shown as n (%).

*Objective confirmation in 22 of 25 patients (14 of 16 rechallenged patients).

find an association with TPMT status, but were limited by incomplete reporting of TPMT status and lack of a control group.[3] As only 20% of hypersensitive patients had reduced TPMT activity, TPMT deficiency is not required for the development of azathioprine hypersensitivity. More likely, reduced TPMT activity is a susceptibility factor resulting in prolonged exposure of azathioprine, 6-MP, or another metabolite responsible for the response, to T cells. Importantly, TPMT deficiency by itself is not sufficient to develop azathioprine hypersensitivity.

Finally, all patients with azathioprine hypersensitivity were using prednisolone at the time of their hypersensitivity reaction, meaning that low- to medium-dose prednisolone use (up to 30 mg/day in this study) does not (sufficiently) protect against the occurrence of this clinical syndrome.

The mechanism of azathioprine hypersensitivity has not yet been elucidated. Based on the low dose (25 mg) required for rechallenge and normal TPMT in most (80% of) patients, it is most likely dose independent (type B).[18] Based on the time course at the first exposure and rechallenge and the frequent presence of neutrophilia, it is most likely either a type IVd hypersensitivity reaction (T-cell mediated, with involvement of neutrophils)[19] or a direct pharmacologic interaction of the drug or a metabolite to an immune receptor (p-i reaction).[18]

In this study, we describe azathioprine hypersensitivity in a large observational cohort, resulting in more accurate estimation of the frequency of azathioprine hypersensitivity and distribution of symptoms compared with previous studies. Also, 16 (64% of) patients had a confirmation of azathioprine hypersensitivity through rechallenge with a low dose of azathioprine, allowing for a more reliable description of symptoms. The similar distribution of symptoms in patients with and without rechallenge indicates that patients with azathioprine hypersensitivity have been adequately selected in this study.

This study also has some limitations. First, not all patients received an in-hospital laboratory evaluation during their

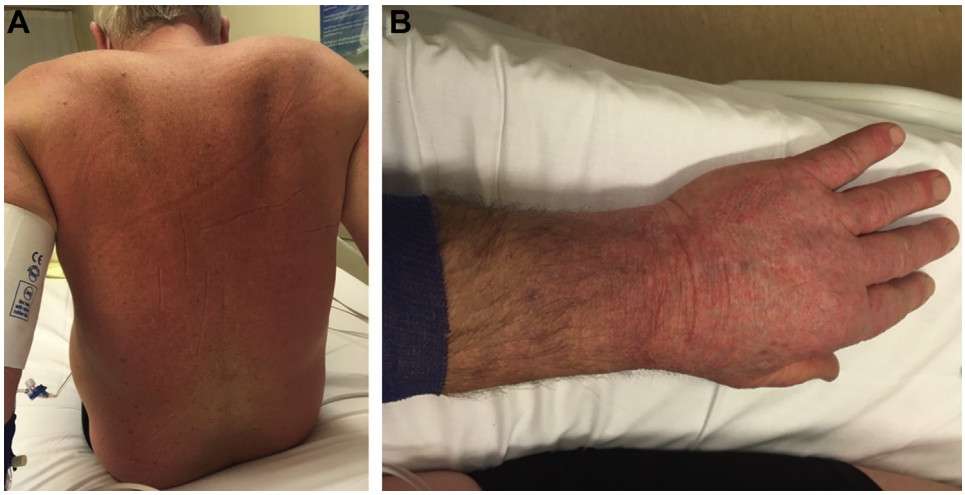

FIGURE 1. Picture of skin involvement in azathioprine hypersensitvity. Skin eruption in a 65-year-old patient with GPA with azathioprine hypersensitivity. He developed malaise, fever, nausea, and vomiting 2.5 weeks after starting azathioprine. On physical examination, a maculopapular exanthema was seen (**A**), which was most pronounced on the backs of his hands and feet (**B**). The pathology report described superficial lymphocytic and neutrophilic granulomatous inflammation, without micro-organisms or vasculitis. *GPA*, Granulomatosis with polyangiitis.

TABLE III. Laboratory findings of patients with azathioprine hypersensitivity

		CRP (mg/L)		Leukocytes (10^9/L)		Neutrophils (10^9/L)		Eosinophils (10^9/L)	
Patient no., sex, age (y)	Diagnosis, ANCA type	Before reaction	With reaction	Before reaction	With reaction	Before reaction	With reaction	Before reaction	With reaction
1, M, 45	MPA, MPO	↑7	↑315	4.8	9.8	3.66	↑9.10	0.13	0.03
2, M, 57	GPA, PR3	↑11	↑222	5.9	9.4	NA	NA	NA	NA
3, F, 69	EGPA, MPO	↑31	↑112	5.5	6.6	3.97	5.16	↑0.44	0.40
4, M, 56	MPA, MPO	↑40	↑390	8.5	↑17.0	7.18	↑16.48	0.00	0.00
5, M, 45	GPA, PR3	<5	↑327	9.6	9.7	↑8.34	↑8.38	0.03	0.03
6, M, 65	MPA, MPO	↑21	↑225	3.8	8.9	2.67	↑7.55	0.00	0.01
7, M, 49	GPA, PR3	<5	↑125	6.3	↑11.5	4.87	↑10.19	0.03	0.08
8, F, 74	MPA, MPO	<5	↑194	5.0	8.7	4.33	↑8.00	0.00	0.03
9, M,73	GPA, PR3	↑20	↑166	8.5	7.7	7.07	6.15	0.03	0.19
10, M,47	GPA, PR3	<5	↑25	5.6	3.8	5.21	NA	0.02	NA
11, M,46	GPA, PR3	<5	↑22	9.9	9.4	↑8.83	NA	0.00	NA
12, F, 59	MPA, MPO	<5	↑34	↑10.8	↑10.1	↑9.36	↑8.61	0.14	0.43

↑, Elevated according to local reference values; *ANCA*, antineutrophil cytoplasmic antibody; *CRP*, C-reactive protein; *EGPA*, eosinophilic granulomatosis with polyangiitis; *GPA*, granulomatosis with polyangiitis; *MPA*, microscopic polyangiitis; *MPO*, myeloperoxidase; *NA*, not available; *PR3*, proteinase 3.

hypersensitivity reaction, making it difficult to draw solid conclusions regarding laboratory abnormalities associated with azathioprine hypersensitivity. Second, descriptions of azathioprine hypersensitivity symptoms were collected retrospectively, making them dependent on reporting in the electronic patient records. Third, the frequency of azathioprine hypersensitivity in this cohort might be underestimated due to the strict definition requiring fever or due to misdiagnosis as infection or disease relapse. Fourth, no biopsies were performed and descriptions were limited for most hypersensitive patients with skin rash, making it difficult to accurately classify the skin reactions in this cohort. Finally, we did not perform an lymphocyte transformation test with azathioprine to strengthen our hypothesis of a type IV hypersensitivity reaction.

In conclusion, azathioprine hypersensitivity is more frequent than previously mentioned and results in less effective maintenance of disease remission, at least in ANCA-associated vasculitis. Symptoms of azathioprine hypersensitivity reflect systemic inflammation and must be distinguished from disease relapse and infection. Many patients experience an increase in neutrophil counts. The reaction can occur despite (low- to medium-dose) prednisolone therapy.

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