Severe Myelosuppression Following Alopecia Shortly after the Initiation of 6-Mercaptopurine in a Patient with Crohn’s Disease

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Abstract

A 15-year-old, woman, Crohn’s disease patient, who carried the TPMT *3C heterozygous mutant, complained of alopecia 3 days after starting 6-mercaptopurine (6-MP) and then developed severe myelosuppression 6 weeks after starting 6-MP. The alopecia involved scalp hair only (body hair preserved) and was dominant in the temporal region. Following these side effects, transient remission of Crohn’s disease occurred. Myelosuppression due to 6-MP is a rare but life-threatening side effect that is difficult to predict despite continuous monitoring of complete blood cell counts. In the present case, 6-MP-induced alopecia preceded myelosuppression and progressed rapidly as the myelosuppression worsened.

Key words: Crohn’s disease, 6-mercaptopurine, myelosuppression, alopecia, TPMT

Case Report

A 15-year-old woman complained of abdominal pain, diarrhea, bloody stool, and high fever in February 2007. Clinical examination revealed right lower quadrant abdominal tenderness, anal fissure, and erythema nodosum. Colonoscopy showed longitudinal ulcers and a cobblestone appearance from the ascending to the sigmoid colon. Barium enema showed longitudinal ulcers in the ileum. She was diagnosed as having Crohn’s disease (CD) (small and large bowel type). Mesalazine 3 g/day with enteral nutrition (EN) led to clinical remission one month after her first visit. However, she refused further EN. Therefore, several relapses, including abdominal pain and diarrhea with high fever, occurred in the short term. 6-mercaptopurine (6-MP) 30 mg/day was started with good effect. She noticed alopecia that was dominant in the temporal region and showed preservation of the total hairline area 3 days after starting 6-MP. The degree of alopecia was mild; it was obvious to her but not to others, which was why she did not stop taking 6-MP and did not see a doctor immediately. Then, 6 weeks after starting 6-MP, her hemoglobin level (Hb) decreased to 7.5 g/dL. Since myelosuppression due to 6-MP was suspected, 6-MP was discontinued. Six days after discontinuation of 6-MP, she had a fever of 39.0°C. Blood tests showed WBC 1,190/μL, neutrophils 214/μL, RBC 241×10⁴/μL, Hb 6.7 mg/dL, Ht 19.2%, Plt 3.1×10⁴/μL, and CRP 1.71 mg/dL. No atypical blood cells were seen. Genotype analysis by real time PCR showed thiopurine S methyltransferase (TPMT)*1/*3C. Mesalazine was stopped so as to not inhibit TPMT. The greatest scalp hair loss occurred about the nadir of myelosuppression (WBC 960/μL, neutrophils 182/μL) and was facilitated by insults to the hair, such as use of shampoo. The patient was treated with filgrastim 133 μg/day, broad-spectrum antibiotics, and blood transfusions. She recovered from the myelosuppression 2 weeks after stopping 6-MP. Mesalazine 1.5 g/day was restarted. However, her alopecia continued for 6 weeks. Despite stopping 6-MP, clinical remission continued without EN for 18 weeks (Fig. 1). After the episode, frequent clinical relapses led to infliximab therapy, which induced remission.

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Figure 1. Clinical course. The patient complained of alopecia 3 days after starting 6-MP and then developed severe myelosuppression 6 weeks after starting 6-MP. However, the patient recovered from myelosuppression 2 weeks after stopping 6-MP, though the alopecia continued for 6 weeks. After the development of these side effects, the patient achieved transient remission of her CD and continued without EN for 18 weeks.

Discussion

In the present case, alopecia developed shortly after the initiation of 6-MP before the development of severe myelosuppression. 6-MP has been known to be effective in inducing and maintaining remission in patients with CD (1, 2). However, 6-MP is a cytotoxic agent that attacks rapidly dividing cells in the body, including the dividing hair matrix cells and hematopoietic cells. Myelosuppression is one of the most serious side effects of 6-MP, but it is symptomatic only after it becomes severe. In a retrospective study of patients with inflammatory bowel disease receiving 6-MP, 2% developed severe bone marrow suppression requiring hospitalization, with leukocyte counts ranging from 300 to 2,500/µL (3). Even with continuous monitoring of the complete blood cell counts (CBC), myelosuppression sometimes cannot be predicted.

We have previously treated two other inflammatory bowel disease patients who received azathioprine (AZA), a prodrug of 6-MP, and developed severe alopecia (almost bald) and severe myelosuppression as a side effect of AZA. One case was a 36-year-old man with CD who complained of alopecia and developed severe myelosuppression almost simultaneously 3 weeks after starting AZA. The other case was a 23-year-old woman with ulcerative colitis who developed severe myelosuppression 2 weeks after starting AZA and then later complained of alopecia. In our experience, the interval between the start of these drugs and the development of alopecia varies between 3 days to 1 month. Awareness of alopecia may vary between individuals. Furthermore, short-haired men may have more difficulty than long-haired women in noticing alopecia early. This may be one of the reasons why there were considerable variabilities in the timing of alopecia and myelosuppression caused by 6-MP or AZA. In the first case, alopecia preceded myelosuppression. Judging from the role of leukopenia in the 6-MP-induced remission of refractory CD (4), it is expected that mild alopecia may occur in cases where 6-MP is effective, and alopecia may progress rapidly as the myelosuppression worsens.

Alopecia totalis (body hair preserved) and alopecia universalis (a generalized loss of all body hair) are rare extra-intestinal symptoms of CD (5, 6), for which immunomodulatory therapy with AZA has been reported to be beneficial, though not all authors agree (6). Chemotherapy-induced alopecia (CIA) is mainly anagen effluvium, and it most commonly affects scalp hair (7). The anagen hairs that grow actively are mostly located on the inner side of the scalp hairline. On the other hand, telogen hairs in the period of dormancy are located in the scalp hairline. Therefore, CIA presents as patterned hair loss that spares the scalp hairline (8). Chemotherapy attacks dividing hair matrix cells and causes thinning of the hair shaft. As a result, the hair shaft may break at the follicular orifice by an insult, such as touching a pillow or use of shampoo. In the present case, marked hair loss in the temporal region was probably caused by touching a pillow. Alopecia usually begins 7-10 days after the initiation of a cytotoxic agent, and hair regrowth begins several weeks after the cessation of drug therapy (8). Therefore, the differential diagnosis of drug-induced alopecia and alopecia as a complication of CD might be easily made based on the presence or absence of previous cytotoxic agent treatment and the appearance of each type of alopecia.
6-MP is metabolized by three competing routes (9). 6-MP is first metabolized by hypoxanthine-guanine phosphoribosyl transferase into thioguanine nucleotide (TGN), which has immunosuppressant activity. A second catabolic route, which has little inter-individual variation, is oxidation by xanthine oxidase. Lastly, in a major catabolic pathway, TPMT enzyme converts 6-MP into the inactive form. Inter-individual variation in TPMT activity is significantly larger because of genetic polymorphism. Few mutant alleles other than TPMT*3C are found in Japan and China. The prevalence of TPMT*3C is 0.8-1.6%, and the genotype is *1/*3C only in Japan (10, 11). As compared with the wild type, TPMT activity was about 25% lower in a *1/*3C heterozygous mutant (12). Lennard reported that knowledge of TPMT status warned of early bone marrow toxicity during the initial months of AZA therapy (13). However, the effectiveness of initial testing for TPMT polymorphism remains uncertain. The 6-MP-induced severe myelosuppression in the present case may have been associated with a TPMT*3C heterozygous mutation.

References