ALLOPURINOL — INDUCED SKIN REACTIONS AND AGRANULOCYTOSIS

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SYNOPSIS

The association of allopurinol and agranulocytosis is rare. The twin association of agranulocytosis and skin reaction with allopurinol has never been reported before. We present here a woman who developed a skin rash and fatal agranulocytosis after allopurinol therapy. Allopurinol-induced skin rash is a hypersensitivity phenomenon. The mechanism of the agranulocytosis is myeloid depression due possibly to an idiosyncratic reaction.

INTRODUCTION

Allopurinol-induced agranulocytosis is uncommon. Reported cases have been seen in patients with underlying metabolic disturbances due either to cirrhosis of the liver (1), diabetes mellitus (2) or starvation (3). The outcome is invariably fatal although reversibility has been reported in cases of less severely associated neutropenia (3). Cutaneous manifestations associated with allopurinol therapy is a relatively common hypersensitivity phenomenon. The combination of cutaneous hypersensitivity and renal manifestations following allopurinol treatment is known (4). The twin association of agranulocytosis and skin hypersensitivity reaction with allopurinol, however, has not been reported before. We present here an elderly woman with this unusual combination of allopurinol adverse reactions.

CASE REPORT

A 71 year old Chinese woman was seen in the University Department of Medicine, Singapore General Hospital in February 1980 for the complaint of painful knees. She was found to have severe osteoarthritis of both knees and was referred to the Orthopaedic Clinic where she was seen on 12 February 1980. She was prescribed mefenamic acid. On 26 February 1980 mefenamic acid was discontinued and she was prescribed allopurinol and aspirin. The serum uric acid level was 8.3 mg/dl (Normal: 3.7 - 7.6 mg/dl) and serum creatinine 1.2 mg/dl (Normal: 0.5 - 1.6 mg/dl). Twenty-four

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days later, on 21 March 1980, she was admitted with fever, swelling of the face and a generalized, pruritic, maculopapular rash. Allopurinol and aspirin were stopped immediately and prednisolone was prescribed. The fever subsided and the rash improved. She was discharged after 6 days.

The patient had mild diabetes mellitus controlled on diet alone. She also had essential hypertension for many years during which she took hydrallazine irregularly. On 28 March 1980, two days following discharge from hospital, she was readmitted with diarrhoea and giddiness. There was a residual generalized maculopapular rash. The blood pressure was 120/90 mmHg. The total white cell count was 6,100/cu mm with 67% neutrophils. She was afebrile. She developed a fever on 3 April 1980. The total white cell count dropped to 1,000/cu mm with only 7% neutrophils. She received gentamicin, carbenicillin, crystalline penicillin and granulocyte concentrates despite which she remained febrile. Blood cultures grew proteus mirabilis sensitive to gentamicin. A bone marrow aspirate performed on 8 April 1980 revealed a hypocellular marrow with decreased megakaryocytes, diminished erythropoiesis and an almost total absence of granulocyte precursors. She died the same day.

DISCUSSION

Allopurinol-induced agranulocytosis is due to myeloid depression (1, 2). Interestingly, our patient showed not only myeloid depression but also decreased megakaryocytes and red cell precursors although the latter two were less severely affected. Terminally, there was a fall in the platelet count but the hemoglobin remained unaffected throughout. The latter observation is explained by the longer life-span of erythrocytes in comparison to those of the platelets and neutrophils.

The development of a rash three and a half weeks following commencement of allopurinol therapy is typical of allopurinol skin hypersensitivity (4). The interval of two weeks between cessation of allopurinol and the development of severe neutropenia in our patient was probably a reflection of her marrow granulocyte storage reserve. The subsequent rapid deterioration with severe neutropenia was aggravated by the development of a Gram negative septicemia due to proteus mirabilis. Despite prompt and appropriate antibiotic coverage as well as white cell support she succumbed to the septicemia.

The mechanism for allopurinol-induced marrow depression is not known. Just as the skin reaction is a hypersensitivity phenomenon (4), perhaps the associated agranulocytosis is due to an idiosyncratic reaction to allopurinol or one of its metabolities. The rarity of allopurinol-induced agranulocytosis favours an idiosyncratic type reaction.

Allopurinol ribonucleotide, a metabolite of allopurinol, can potentially inhibit purine and pyrimidine biosynthesis (1, 5). It is speculative that this may be the mechanism responsible for marrow depression. Such an effect would mimic that of antimetabolites such as 6-thioquanine and 6-mercaptopurine. However, whereas marrow depression due to antimetabolites is dose dependent, that due to allopurinol is unpredictable and dose unrelated. This argument together with the rarity of allopurinol-induced agranu-

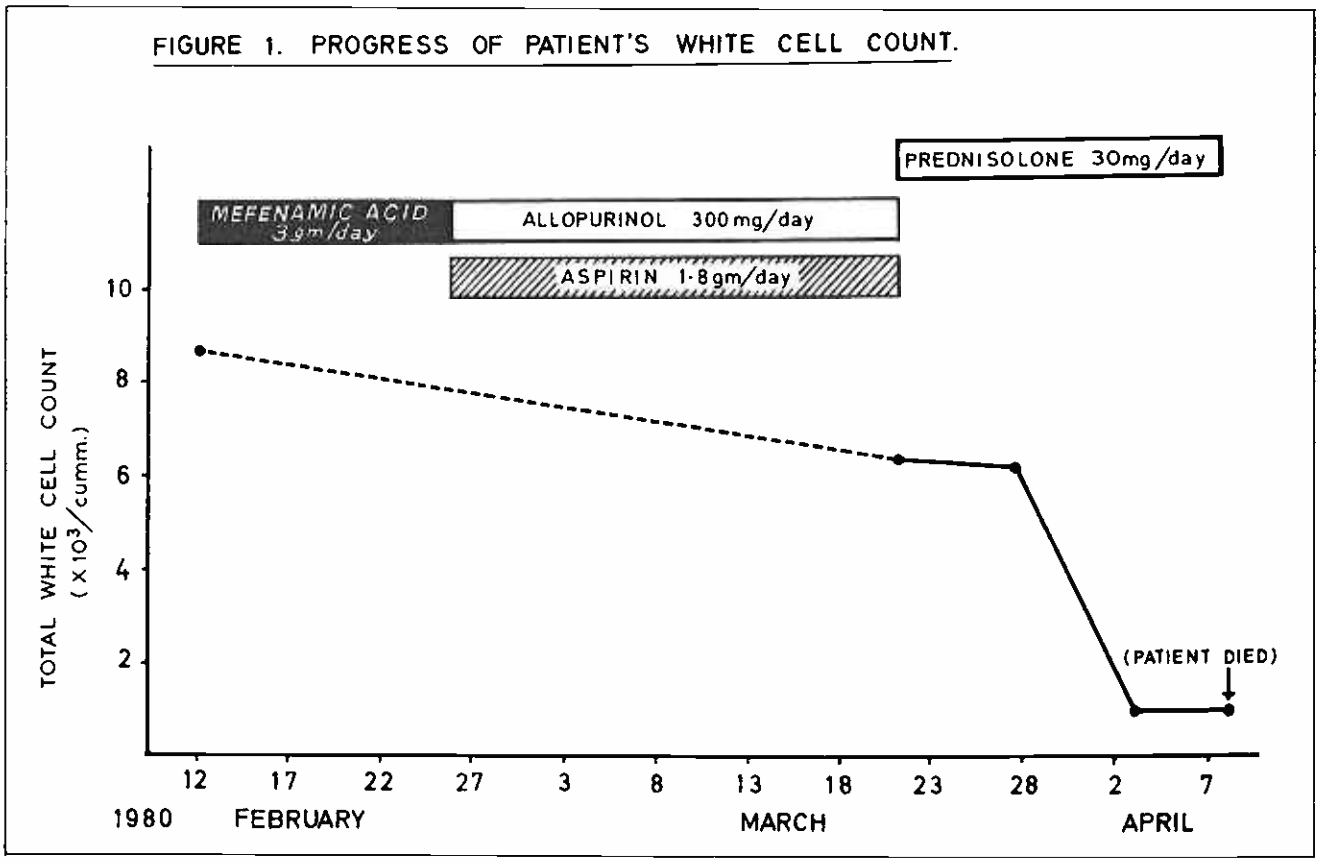

Figure 1. The progress of the patient's white cell count.

locytosis favours hypersensitivity as the mechanism for the marrow depression.

The outcome of allopurinol-induced agranulocytosis is invariably fatal. Reversible cases have been recorded in patients with less severe neutropenia (3). In view of this potential adverse reaction, allopurinol should be used with caution particularly in patients with associated metabolic disorders (1, 2). Ideally granulocyte count should be monitored on all new patients receiving allopurinol treatment. However, since this adverse reaction is uncommon, the overall benefit of such a routine does not justify the cost. We recommend that close monitoring of granulocyte count be considered in those patients with metabolic disturbances when first prescribed allopurinol.

ACKNOWLEDGEMENT

We are indebted to Professor P.K. Wong, Department of Medicine, National University of Singapore, for his comments and advice on the manuscript.

REFERENCES

1. Greenberg MS and Zambrano SS: Aplastic agranulocytosis after allopurinol therapy. Arth Rheum 1972; 15: 413-6.
2. Wilkinson DG: Allopurinol and agranulocytosis. Lancet 1977; 2: 1282-3.
3. Scobie IN, MacCuish AC, Keeson CM and McNeil IR: Neutropenia during allopurinol treatment in total therapeutic starvation. Br Med J 1980; 280: 1163-4.
4. Chan HL, Ku G and Khoo OT: Allopurinol associated hypersensitivity reactions: cutaneous and renal manifestations. Aust NZ J Med 1977; 7: 518-22.
5. Fox IH, Wyngaarden JB and Kelly WN: Depletion of erythrocyte phosphoribosylpyrophosphate in man; a newly observed effect of allopurinol. N Engl J Med 1970; 283: 1177-82.
6. Rundles RW, Metz EN and Silberman HR: Allopurinol in the treatment of gout. Ann Intern Med 1966; 64: 229-58.
7. Yu TF and Gutman AB: Effect of allopurinol on serum and urinary uric acid in primary and secondary gout. Am J Med 1964; 37: 885-98.