Pediatr Nephrol
DOI 10.1007/s00467-014-2849-9

CLINICAL QUIZ

New-onset bone marrow aplasia in a 15-year-old adolescent with pauci-immune crescentic glomerulonephritis: Answers

Chiara Kessler · Sybille Tschumi · Giacomo D. Simonetti · Mario G. Bianchetti

Received: 10 March 2014 / Revised: 24 April 2014 / Accepted: 7 May 2014

Keywords Glomerular disease · Renal impairment · Bone marrow aplasia · Pancytopenia · Adolescent · Azathioprine · Thiopurine-methyltransferase deficiency

Answers

In this adolescent, the causes of acquired bone marrow aplasia that deserve discussion include (1) the condition underlying his glomerular disease, (2) viral infections, and (3) drugs including candesartan and azathioprine [1, 2]. Bone marrow aplasia is uncommon in systemic small vessel vasculitides, including Wegener granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome, the most common conditions that are associated with a pauci-immune crescentic glomerulonephritis. However, leucopenia, thrombocytopenia, and anemia sometimes occur in multisystemic diseases such as systemic lupus erythematosus. In our case, however, the biopsy findings and the autoantibody pattern argue against this diagnosis.

Certain viruses can cause bone marrow aplasia. The best documented is parvovirus B19, which more commonly causes transient red cell aplasia and more rarely pancytopenia. Hepatitis viruses, cytomegalovirus virus, and human immunodeficiency virus can also cause severe aplasia. In our patient, microbiology studies for the mentioned agents were negative. Finally, a causal link between influenza A virus and pancytopenia has been often suspected but almost never demonstrated.

Candesartan has never been associated with pancytopenia. Mild bone marrow suppression is a common side effect of azathioprine, but severe suppression with pancytopenia is uncommon [3, 4]. This agent results in mild leukopenia and thrombocytopenia in ≤25 % and ≤5 % of patients, respectively. These abnormalities usually respond to a reduction in the daily dose of azathioprine. In our patient, laboratory findings of bone marrow suppression persisted and even worsened after the azathioprine dose was decreased by half.

Following intestinal absorption [see Fig. 1], azathioprine is converted to 6-mercaptopurine, which is in turn metabolized to active metabolites by hypoxanthine-guanine-phosphoribosyltransferase and to inactive metabolites by xanthine-oxidase and thiopurine-methyltransferase [3–5]. Not surprisingly, therefore, the bone marrow suppression induced by azathioprine is enhanced by xanthine-oxidase inhibitors and in subjects with congenitally reduced or absent activity of thiopurine-methyltransferase. The frequency of reduced activity and absent activity is approximately 10 and 0.3 % among Caucasian and African ethnic groups, respectively. In Asians, deficiencies occur less frequently [5]. Clearly, patients with reduced or absent thiopurine-methyltransferase activity will not tolerate standard azathioprine doses; consequently, it has been suggested that the former patients should be given one-half or one-third of the standard dose and that the drug should be avoided entirely in patients without enzyme activity [5].

In our adolescent patient, thiopurine-methyltransferase activity in erythrocytes was undectectable. Hence, azathioprine was replaced by mycophenolate mofetil, another inhibitor of purine synthesis, whose prescription does not put patients with a thiopurine-methyltransferase deficiency at risk. The

This refers to the article that can be found at 10.1007/s00467-014-2850-3.

C. Kessler · M. G. Bianchetti (✉)
Pediatric Department of Southern Switzerland, Ospedale San Giovanni, 6500 Bellinzona, Switzerland
e-mail: mario.bianchetti@pediatrician.ch

C. Kessler · S. Tschumi · G. D. Simonetti
Pediatric Nephrology, University of Berne, Berne, Switzerland

Published online: 01 July 2014

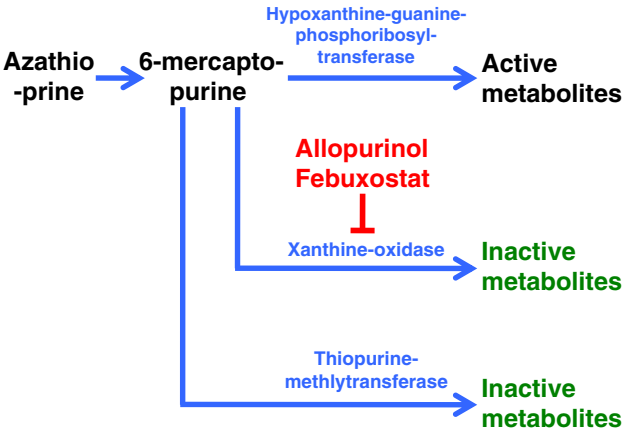

Fig. 1 Metabolism of azathioprine. After intestinal absorption, azathioprine is rapidly converted to 6-mercaptopurine, which in turn is metabolized into active metabolites by hypoxanthine-guanine phosphoribosyltransferase and into inactive metabolites by xanthine oxidase and thiopurine methyltransferase. Bone marrow suppression is enhanced upon treatment with the xanthine oxidase inhibitors allopurinol or febuxostat and in subjects lacking or with reduced thiopurine-methyltransferase activity

subsequent clinical course was favorable, with full recovery from both pancytopenia and respiratory disease.

Thiopurine-methyltransferase (TPMT) is encoded by a gene localized to chromosome 6p22.3 [5]. Four major variant alleles (*TPMT*2*, *TPMT*3A*, *TPMT*3B*, *TPMT*3C*) have been identified, which account for ≥80 % of subjects with absent or reduced enzyme activity. In our patient, genotyping disclosed a homozygous genotype mutant, *TMPT*3A*.

Finally, it is worthy of mention that very high thiopurine-methyltransferase activity predicts treatment failure in patients on azathioprine (likely because these patients are probably underdosed and might instead achieve complete remission on doses of azathioprine higher than those generally recommended).

Commentary

Azathioprine is the cornerstone of maintenance therapy in many chronic conditions [3,4]. Despite our increasing knowledge of bone marrow aplasia, dose adjustment in accordance with the white blood cell count remains the standard of care. The present case demonstrates that treating patients who completely lack thiopurine-methyltransferase activity with azathioprine (like with mercapotpurine or thioguanine) may be hazardous. As a consequence, determination of thiopurine-methyltransferase activity or genotype (genotyping is not susceptible to transfusion effects) might decrease the risk of an adverse drug reaction. Some data indicate that this approach might be cost effective [5, 6].

Financial disclosure None.

Conflicts of interest None.

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