

Bone marrow suppression with plasma cell leukemia-like reaction complicated by macrophage activation syndrome after metamizole overuse

To the Editor We would like to present a case involving a 19-year-old man with bone marrow suppression and preliminary diagnosis of plasma cell leukemia after metamizole overuse. Prior to this diagnosis, our patient was healthy and did not use any medication on a regular basis. However, he recently suffered from a toothache and took from 0.5 to 2 g/d of metamizole for 3 weeks. After this time, he observed severe sore throat, cough, fever, and muscle aches. He continued metamizole but this time in combination with ibuprofen (400–600 mg/d). A week later, the symptoms deteriorated and a general practitioner prescribed him azithromycin, followed by cefuroxime, both without improvement. Finally, after 5 weeks of overuse of nonsteroidal anti-inflammatory drugs, our patient was admitted to the hospital for further diagnostic evaluation and treatment.

On admission to the hospital, fever, tachycardia, palpable and painful peripheral lymph nodes, enlarged tonsils with purulent plugs, multiple aphthae on the oral mucosa, and dental caries were observed. Laboratory tests showed leucopenia (1100/ μ l) and lymphopenia (900/ μ l) with normal hemoglobin levels and platelet count, and high levels of inflammatory markers (C-reactive protein, 255.7 mg/l; procalcitonin, 1.79 ng/ml). During hospitalization, red and white blood cell counts lowered and were accompanied by liver damage and prolonged thrombin and prothrombin time. Uncommon viral (hepatitis B virus, hepatitis C virus, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus) and syphilis infections as well as autoimmune diseases were excluded. All microbiological tests, including blood urine and throat swab cultures, were negative. Bone marrow aspiration revealed isolated granulocyte aplasia with plasma cells constituting 30% of the cells. The patient was transferred to the Hematology Unit with suspicion of plasma cell leukemia.

The patient was initially in good condition but showed radiologic signs of pneumonia and maxillary sinusitis. He was referred to a dentist who removed all caries in teeth, but despite using wide-spectrum empiric antibiotics (ceftazidime, clarithromycin, meropenem, and vancomycin) his clinical condition worsened and blood pancytopenia developed. A bone marrow biopsy showed suppression of all lines with 35% of reactive plasma cells (FIGURE 1A), while in blood smears only single plasma cells were present (FIGURE 1B). These findings suggested inflammatory or reactive etiology of the pathology. Active tuberculosis of the bone marrow was also excluded but the serologic blood test showed elevated levels of parvovirus B19-specific IgM antibodies. We administered granulocyte colony-stimulating factor for 5 days, but leukopenia persisted. For this reason, a second bone marrow biopsy was performed, which demonstrated bone marrow regeneration but with signs of macrophage activation and hemophagocytosis (FIGURE 1C). This finding was consistent with the laboratory characteristics of liver damage and coagulation abnormalities. Macrophage activation syndrome (MAS) was diagnosed and corticosteroids were prescribed (dexamethasone 3 $\times$ 8 mg/d for 5 days, followed by prednisone 1 mg/kg/d). This resulted in a rapid clinical and laboratory improvement. A week later, bone marrow aspirate was normal. Systemic steroids were tapered for the next 3 weeks and finally stopped. Four weeks after discharge, the patient was healthy, did not take any medications, and his laboratory results were normal (including blood cell counts and inflammatory markers).

The most likely cause of bone marrow suppression in our patient was the metamizole abuse because this medication had been taken for 5 weeks (with about 30 g of cumulative dose). Metamizole is a commonly used nonsteroidal anti-inflammatory drug that is prohibited in many countries due to the risk of agranulocytosis. In Poland, it is still available without prescription. A national safety

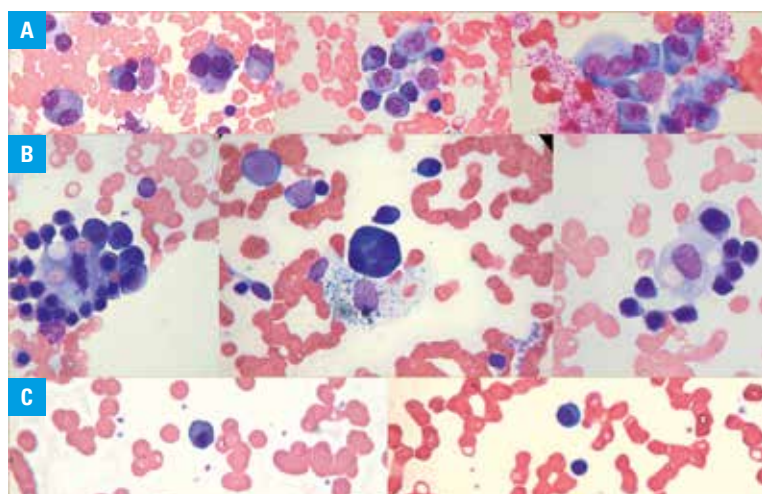


FIGURE 1 Bone marrow aspirate and peripheral blood smears: 35% infiltration of reactive plasma cells in the bone marrow (A); single plasma cells and red cells in the peripheral blood (B); activated macrophages in the bone marrow (C); Wright's stain, magnification $\times 1000$

survey in Poland showed that the risk of agranulocytosis was low (0.16 cases per million person-days of use).¹ In Sweden, its prevalence was estimated as 1 per 31,000 patients treated with metamizole in the hospital and 1 per 1400 outpatients.² In our patient, the large cumulative dose of metamizole might have been critical. We cannot also exclude the contribution of parvovirus B19 (a common virus transmitted via the respiratory tract) to bone marrow damage and development of MAS.

Viral or bacterial respiratory tract infections are associated with a wide range of extrapulmonary manifestations.³ Parvovirus B19 can lead to transient aplastic and chronic anemia, depending on the host.⁴ MAS or secondary hemophagocytic lymphohistiocytosis (HLH) is a severe and life-threatening complication observed mainly in patients with autoimmune diseases or viral infections.⁵ The diagnosis is made when 5 of 8 conditions are fulfilled: 1) fever, 2) splenomegaly, 3) cytopenia in at least 2 cell lines, 4) hypertriglyceridemia and/or hypofibrinogenemia, 5) tissue presentation of hemophagocytosis, 6) low or absent natural killer-cell activity, 7) serum ferritin concentration $>500 \mu\text{g/l}$, and 8) elevated levels of soluble CD25 >2 standard deviations above the mean (usually $>2400 \text{ IU/ml}$). HLH treatment depends on the severity and cause of the disease, but steroids with or without cyclosporine are usually required.⁵

We hope that the presentation of this case will help raise awareness of potential harmful side effects of metamizole, a widely used nonsteroidal anti-inflammatory drug, currently available in Poland over the counter.

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Author names and affiliations Artur Jurchyszyn, Anna Engel, Stanisława Bazan-Socha, Jacek Czepiel, Grażyna Biesiada, Aleksander B. Skotnicki (A.J., A.B.S.: Department of Hematology, University Hospital, Kraków, Poland; A.E.: Department of Electrophysiology, John Paul II Hospital,

Kraków, Poland; S.B.: 2nd Department of Internal Medicine, Jagiellonian University Medical College, Kraków, Poland; J.C., G.B.: Infectious Disease Clinic, Jagiellonian University Medical College, Kraków, Poland

Correspondence to: Artur Jurchyszyn, MD, Klinika Hematologii, Szpital Uniwersytecki w Krakowie, ul. Kopernika 19, 31-501 Kraków, Poland, phone/fax: +48-12-424-74-26, e-mail: mmjucz@cyf-kr.edu.pl.

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