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SHORT REPORT

Aplastic anemia in a lung adenocarcinoma patient receiving pemetrexed

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Summary Pemetrexed (PEM) is an antimetabolite drug that interferes with enzymes involved in DNA synthesis and also the folate-dependent metabolic processes necessary for DNA replication and homocysteine homeostasis. Continuation maintenance with PEM after induction therapy with PEM plus cisplatin has been the standard form of first-line chemotherapy for advanced non-squamous non-small cell lung cancer. The regimen has a low incidence of bone marrow suppression, and the incidences of anemia, leukopenia, neutropenia and thrombocytopenia exceeding grade 3 are less than 5%. Here we report a 68-year-old Japanese man with stage IIIB (cT4N3M0) lung adenocarcinoma who received 4 cycles of chemotherapy with PEM 500 mg/m^2 and cisplatin 75 mg/m^2 every three weeks, which resulted in a partial response, and then continued to receive maintenance PEM monotherapy. After 11 cycles of PEM maintenance therapy, the patient's platelet count decreased, and progressed to pancytopenia within two months. A bone marrow puncture revealed replacement with fatty marrow. As other diseases possibly responsible for pancytopenia were ruled out, we diagnosed the patient as having aplastic anemia. This is the first reported case of aplastic anemia to have occurred during PEM therapy. Clinicians should bear in mind that PEM can potentially trigger severe pancytopenia, including aplastic anemia.

Keywords Aplastic anemia · Pancytopenia · Pemetrexed · Lung cancer

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Background

Continuation maintenance with pemetrexed (PEM) after induction therapy with PEM plus cisplatin has been the standard first-line chemotherapy for advanced non-squamous non-small cell lung cancer (NSCLC) [1]. The regimen is associated with a low incidence of bone marrow suppression, and the incidence of anemia, leukopenia, neutropenia and thrombocytopenia exceeding grade 3 is less than 5% [1]. Here, we describe a case of severe pancytopenia, diagnosed as aplastic anemia, that occurred during PEM maintenance therapy.

Case report

A 68-year-old Japanese man who had 50 pack years of tobacco exposure was diagnosed as having stage IIIB (cT4N3M0) lung adenocarcinoma in September 2013. He had been taking several medicines, including folic acid, flunitrazepam, sulpiride and magnesium oxide. He and his family had no history of hematological disease. He received 4 cycles of chemotherapy with PEM 500 mg/m^2 and cisplatin 75 mg/m^2 every three weeks, which resulted in a partial response (PR), and then continued with maintenance PEM monotherapy. No bone marrow suppression occurred during chemotherapy. After completion of 11 cycles of PEM maintenance therapy, the patient's platelet count decreased (7.9×10^4/μL), and continued to drop. When the thrombocytopenia had become grade 3, we performed a bone marrow puncture, which revealed hypocellularity and a markedly fatty marrow (Fig. 1a). Despite frequent platelet transfusion, the platelet count continued to decrease, and after two months the patient developed pancytopenia. Computed tomography and positron emission tomography showed no further progression of the

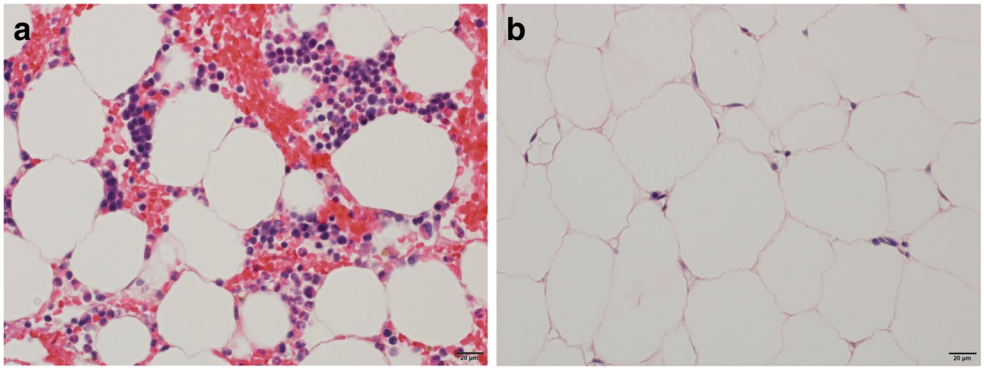

Fig. 1 **a** The first bone marrow sample obtained at 6 weeks after 11 PEM cycles, showing hypocellularity and markedly fatty bone marrow. **b** The second bone marrow sample obtained at 16 weeks after 11 PEM cycles, showing complete replacement by fatty bone marrow

adenocarcinoma, and therefore another bone marrow puncture was undertaken. This showed complete replacement with fatty bone marrow (Fig. 1b). As the patient's serum iron, vitamin-B12, folic acid, and antinuclear antibody levels were normal, the presence of any other underlying disease responsible for the pancytopenia was ruled out. Therefore, we diagnosed the patient as having PEM-induced aplastic anemia. Despite administration of G-CSF, and transfusion of red blood cells and platelets, the pancytopenia was refractory.

Discussion

Aplastic anemia is a rare hemopoietic stem-cell disorder that results in pancytopenia and hypocellular bone marrow. Although most cases of aplastic anemia are acquired, no etiological agent can be identified in most cases, although causal associations with many agents, including drugs, benzene exposure, insecticides, and viruses, have been suggested [2, 3]. A population-based case-control study of aplastic anemia in Thailand found that drugs were the most commonly implicated cause, but they explained only 5% of newly diagnosed cases [2]. We searched the literature and reports of adverse events secondary to PEM using PubMed database, the medical package insert and the drug interview form of the PEM. The present case of acquired aplastic anemia is the first reported example to be linked to PEM, a cytotoxic anti-cancer drug.

PEM is an antimetabolite drug that interferes with the enzymes involved in DNA synthesis, in particular by inhibiting thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. PEM interferes with the folate-dependent metabolic processes necessary for DNA replication and homocysteine homeostasis. Considering that PEM is non-target-specific, the effects of its activity may involve tissues other than lung cancer, such as bone marrow. Methotrexate (MTX) is a folate antagonist which, like PEM, is used in the treatment of various malignancies, autoimmune disorders, and for induction of abortion. MTX has been reported to induce severe pancytopenia, but aplastic anemia has not been reported as a side effect so far [4, 5]. It is possible that the mechanism of pancytopenia induced by PEM is similar to that induced by MTX. The reasons for induction of pancytopenia by MTX are multifactorial [4]. Because of their structural similarity, MTX and folates compete at various stages, especially during cellular uptake, cellular storage as polyglutamates, and binding to enzymes. The ability of MTX to undergo polyglutamation, which alters the spectrum of enzymes inhibited by the drug, is one of several properties that underlie its cytotoxicity. MTX is polyglutamated and retained for a long period in the liver of patients with rheumatoid arthritis [6], as well as in bone marrow myeloid precursors [7]. Accumulation of MTX polyglutamates in the liver reduces the polyglutamation of natural folates in that tissue [8] and may account for the chronic hepatotoxicity associated with MTX. PEM might induce aplastic anemia through a mechanism similar to that of MTX, because of their similar modes of pharmacological action.

Aplastic anemia was originally thought to result from a direct toxic effect on hemopoietic stem cells that led to a decrease in their numbers. Recently, it has been clarified that the pathophysiology of acquired aplastic anemia is immune-mediated in most cases, autoreactive lymphocytes mediating the destruction of hemopoietic stem cells [9]. An autoimmune mechanism may have been operating in the present case, and PEM may have triggered drug-induced aplastic anemia.

Other medicines had a possibility to occur aplastic anemia. No information about pancytopenia and aplastic anemia have reported in the medical package insert and the drug interview form of flunitrazepam, sulpiride and magnesium oxide. In 2008, Pharmaceuticals and Medical Devices Agency has reported that 3 cases who treated with cisplatin occurred aplastic anemia [10]. However, we considered that the relation between cisplatin and aplastic anemia was unlikely, because 9 months passed since he received last treatment of cisplatin.

In conclusion, we have presented a case of aplastic anemia possibly triggered by PEM. Clinicians should bear in mind that PEM can potentially trigger severe pancytopenia, including aplastic anemia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol J-L, Bidoli P et al (2012) Maintenance therapy with PEM plus best supportive care versus placebo plus best supportive care after induction therapy with PEM plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 13:247–255
2. Issaragrisil S, Kaufman DW, Anderson T, Chansung K, Thamprasit T, Sirijirachai J et al (1997) Low drug attributability of aplastic anemia in Thailand. Blood 89:4034–4039
3. Bacigalupo A, Oneto R, Bruno B, Socié G, Passweg J, Locasciulli A et al (2000) Current results of bone marrow transplantation in patients with acquired severe aplastic anemia: report of the European Group for Blood and Marrow transplantation. Acta Haematol 103:19–25
4. Lim AYN, Gaffney K, Scott DGI (2005) Methotrexate-induced pancytopenia: serious and under-reported? Our experience of 25 cases in 5 years. Rheumatology 44:1051–1055
5. Fernando GI, Sahar EM, Shiri S, Hazem A, Amer KS, Simon B, et al. (2014) Methotrexate-induced pancytopenia. Case Reports in Rheumatology 2014: 679580.
6. Kremer J, Galivan J, Streckfuss A, Kamen B (1986) Methotrexate metabolism analysis in blood and liver of rheumatoid arthritis patients. Association with hepatic folate deficiency and formation of polyglutamates. Arthritis Rheum 29:832–835
7. Koizumi S, Curt GA, Fine RL, Griffin JD, Chabner BA (1985) Formation of methotrexate polyglutamates in purified myeloid precursors cells from normal human bone marrow. J Clin Invest 75: 1008–1014
8. Rosenblatt DS, Whitehead VM, Dupont MM, Vuchich MJ, Vera N (1978) Synthesis of methotrexate polyglutamates in cultured human cells. Mol Pharmacol 14:210–214
9. Robert A Brodsky, Richard J Jones (2005) Aplastic anaemia. Lancet 365: 1647–1656.
10. Parmaceuticals and Medical Devices Agency (2008)