

Pemetrexed anaphylaxis—an unusual suspect

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Clinical Implications

- Pemetrexed is an antifolate drug commonly used in combination with other agents and might be an underestimated cause of immediate hypersensitivity. This is the report of pemetrexed anaphylaxis, supporting an IgE-mediated mechanism with positive skin tests and passive histamine release test.

TO THE EDITOR:

Pemetrexed is a folate antimetabolite, chemically related to methotrexate and folic acid, in the thymidylate synthetase inhibitors group. It inhibits several enzymes in folate synthesis, disrupting folate-dependent metabolic processes essential for cell replication.¹

It is approved by Food and Drug Administration and European Medicines Agency to be used in combination with cisplatin to treat malignant pleural mesothelioma in nonresectable and nonsurgical subjects. It is also approved for the treatment of nonsquamous nonsmall cell lung carcinoma.²

Pemetrexed is associated with a low incidence of adverse events including myelosuppression, neutropenic infection, renal failure, interstitial pneumonitis, and radiation recall.²

Hypersensitivity reactions to pemetrexed are described in the medical literature and include 1 case each of acute generalized exanthematous pustulosis and urticarial vasculitis.³ Two cases of epidermal necrolysis³ and 3 of immediate hypersensitivity also have been reported, none of the latter with a documented positive skin test or histamine release test (HRT) to pemetrexed.⁴⁻⁶ However, considering its frequent use in combination with other chemotherapeutic drugs agents, pemetrexed might be an underestimated cause of immediate hypersensitivity reactions during chemotherapy (CMT).

We describe the case of a 51-year-old woman with stage IV metastatic lung adenocarcinoma, scheduled to receive palliative CMT with pemetrexed plus carboplatin; fosaprepitant was scheduled to be given immediately before CMT perfusion for nausea control. During her first treatment cycle, after completing fosaprepitant and carboplatin infusions, and approximately 3 minutes into the pemetrexed infusion, she developed dyspnea, cyanosis of the extremities, a generalized exanthema and pruritus, and diaphoresis. The infusion was immediately stopped, and she was treated with intravenous hydrocortisone, 200 mg, and clemastine, 2 mg. She subsequently developed loss of consciousness and urinary and rectal incontinence, bradypnea (hypopnea), tachycardia (120 bpm), and an undetectable blood pressure.

Intravenous epinephrine, 0.5 mg, and aggressive fluid administration with both crystalloid, 500 mL, and colloid, 500 mL, solutions resulted in rapid improvement. She was discharged, fully

recovered, 24 h after this event. Serum tryptase obtained during the episode was 67.5 µg/L (normal range <11.4 µg/L, patient's baseline: 4.08 µg/L [obtained 6 months after the reaction]).

The patient was referred to the allergy and clinical immunology clinic 6 months later. Skin-puncture tests (SPT) to pemetrexed 25 mg/mL resulted in a 7-mm wheal with a histamine control, 10 mg/mL, in a 5-mm wheal. Her skin test was negative to carboplatin 10 mg/mL and fosaprepitant 1 mg/mL. An intradermal test to pemetrexed (1/1000 = 0.025 mg/mL) was positive, with a 6 mm increase in the original wheal, and negative to carboplatin (1/1000-1/10 = 0.01-1 mg/mL⁷) and fosaprepitant (1/1000-1/10 = 0.001-0.1 mg/mL). She subsequently continued carboplatin and fosaprepitant without consequence. A passive HRT (pHRT) to pemetrexed, performed as described elsewhere,⁸ resulted in the histamine release of 10.2 ng/mL, considered positive (Figure 1).

Histamine release to pemetrexed

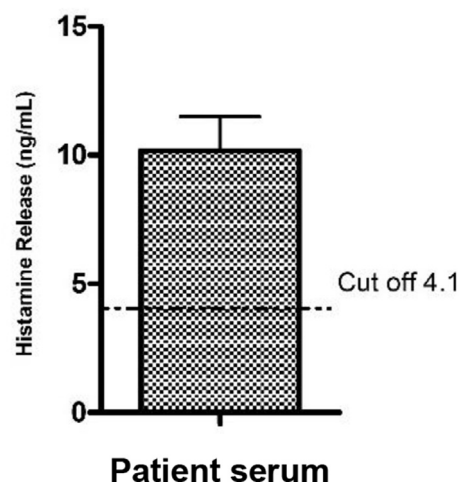


FIGURE 1. Result of the passive histamine release test to pemetrexed. IgE-stripped whole donor blood was passively sensitized by incubation with patient serum, and then incubated in glass fiber—prepared microtiter plates with pemetrexed 25 mg/mL, in the presence of IL-3. Pemetrexed concentration chosen for this test was the highest value that did not lead to nonspecific histamine release (>10 ng/mL) in a dose-response curve. This level corresponded to the mean plus 3 standard deviations of the histamine release values measured in 5 nonallergic subjects without a specific stimulus. Anti-IgE (KPL) at a concentration of 5 µg/mL was used as positive control, as well as histamine at concentrations of 0 and 50 ng/mL. After incubation, the NaOH/ortho-phthalaldehyde (OPA) mixture was added to each well, allowing glass fiber—bound histamine to be released and coupled to OPA. The coupling reaction was stopped, and histamine-OPA complexes were stabilized. Histamine concentrations were determined by fluorometry (Histareader 501 fluorometer [RefLab]) and expressed as ng/mL of histamine released.

The authors conclude that the patient had a Grade IV anaphylactic reaction⁹ to pemetrexed and that it was IgE mediated. Similar SPT (1/1 = 25 mg/mL) and intradermal tests (IDT) (1/100-1/1000 = 0.25-0.025 mg/mL) were performed on 2 subjects previously treated with pemetrexed without consequence. This makes an irritative reaction to a high concentration of this molecule unlikely. SPT and IDT were not performed on subjects not exposed to this medication for ethical reasons.

The clinical characteristics of anaphylaxis, an elevated serum tryptase obtained during the reaction, and the positive skin tests and the pHRT support the fact that the reaction was caused by an immediate IgE hypersensitivity reaction to pemetrexed. Considering the time of administration and the more frequent association of immediate hypersensitivity reaction to platinum salts,¹⁰ carboplatin and fosaprepitant were suspected to be involved. However, negative skin tests and later uneventful administration of both drugs ruled out that possibility.

In conclusion, this is the fourth case of an anaphylactic reaction to pemetrexed and the first with positive skin tests and pHRT supporting of an IgE-mediated mechanism.

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REFERENCES

1. Perez-Moreno MA, Galvan-Banqueri M, Flores-Moreno S, Villalba-Moreno A, Cotrina-Luque J, Bautista-Paloma FJ. Systematic review of efficacy and safety of pemetrexed in non-small-cell-lung cancer. *Int J Clin Pharm* 2014;36:476-87.
2. ALIMTA (pemetrexed for injection) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017. Available from: <http://uspl.lilly.com/alimta/alimta.html#pi>. Accessed November 24, 2017.
3. Piérard-Franchimont C, Quatresooz P, Reginster MA, Piérard GE. Revisiting cutaneous adverse reactions to pemetrexed. *Oncol Lett* 2011;2:769-72.
4. Youk J, Park H, Jin KN, Moon HJ, Yang MS, Kim KH, et al. Successful desensitization of pemetrexed-induced anaphylaxis in a patient with malignant mesothelioma. *Korean J Intern Med* 2017;32:563-5.
5. Shah BK, Hewett Y. Pemetrexed-induced anaphylaxis. *Acta Oncol* 2013;52:881.
6. Capelle H, Birnbaum J, Tomasini P, Tummino C, Gouitaa M, Ausias N, et al. Anaphylactic reaction to pemetrexed: a case report. *J Pharm Pharm Sci* 2014;17:229-30.
7. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013;68:702-12.
8. Arribas F, Falkencrone S, Sola J, Gomez-Serranillos MP, Laguna JJ, Montanez MI, et al. Basophil histamine release induced by amoxicilloyl-poly-L-lysine compared with amoxicillin in patients with IgE-mediated allergic reactions to amoxicillin. *J Investig Allergol Clin Immunol* 2017;27:356-62.
9. Mueller HL. Diagnosis and treatment of insect sensitivity. *J Asthma Res* 1966;3:331-3.
10. Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol* 2010;125(Suppl 2):S126-37.