Eyelid and feet edema induced by pemetrexed

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Abstract:
Pemetrexed is an anti-metabolite that targets multiple enzymes in folate pathway. The main toxicities associated with pemetrexed are asthenia, nausea, diarrhea, myelosuppression, and rash. Few cases of pemetrexed induced cutaneous adverse event have been reported, mainly periorbital-facial edema and edema of the limbs. We report a case of pemetrexed-induced edema of the eyelid and feet in a patient with adenocarcinoma of the lung.

Key words:
Pemetrexed, pharmacovigilance, side effects

Pemetrexed is an anti-metabolite that targets multiple enzymes in the folate pathway. It has been approved for the treatment of nonsmall cell lung cancer and malignant pleural mesothelioma. The main toxicities associated with pemetrexed are asthenia, nausea, diarrhea, myelosuppression, and rash. Few cases of pemetrexed-induced cutaneous adverse events have been reported, mainly periorbital-facial edema.¹,²

We report a case of pemetrexed-induced edema of the eyelid and feet.

Case Report

A 60-year-old woman was diagnosed with adenocarcinoma of the lung in December 2011. She received six courses of pemetrexed from December 2011 to April 2012. The patient received intravenously pemetrexed 500 mg/m² on day 1 every 21 days. Every single dose was preceded 1 week before by intramuscular injection of 1000 μg of Vitamin B₁₂. One week after the sixth dose of pemetrexed, she developed edema on the lower eyelid. This edema improved slowly after 48 h but did not disappear completely. The eyelid edema persisted until the seventh course of pemetrexed in May 2012. One week after this seventh dose, the edema of the lower eyelid worsened, and an edema of the soles of feet appeared. Physical examination did not reveal any other edema or fluid retention. In addition, the patient was neither exposed to overhydration nor suffered from cardiac failure, nephritic syndrome, hypoproteinemia, thyroid dysfunction, or deep venous thrombosis of the superior cava vein. The patient received prednisolone 60 mg daily with improvement of the swelling within 1 week.

The chemotherapy was not modified; a moderate edema of the eyelid appeared whenever a course of pemetrexed was repeated. Prednisolone was taken after each cycle for 7 days.

This case was referred to the Tunisian Pharmacovigilance Center and was analyzed according to the WHO-UMC system for standardized case causality. The causal association of pemetrexed in inducing edema of the eyelid and feet was likely.

Discussion

Fluid retention is an uncommon adverse effect associated with the use of pemetrexed, with an incidence ranging from 14% to 19% for all grades and 1% for grades 3 and 4 in clinical trials. The incidence of periorbital edema is low, and few cases were described in the medical literature.³ Periorbital edema was associated to an ankle edema in one patient and macular erythematous eruption of the trunk in another.¹,² In our case, the edema of eyelid was associated to edema of the soles of feet.

As observed in the present case, the most cases of pemetrexed-induced fluid retention are mild to moderate, and although considered as subjectively unpleasant by the patients, there were not life-threatening and did not have a serious impact on their quality of life.
The mechanism involved in the development of fluid retention and consequent edema is unknown but may be caused by capillary leakage syndrome similarly to that observed with docetaxel.

However, besides docetaxel, tyrosine kinase inhibitors such as imatinib have also been associated with eyelid edema; thus, other pathophysiological mechanisms may be involved with this adverse effect. In the patient who developed edema after using imatinib, the predominant cell population found in the periorbital tissues was normal dendrocytes that are positive for platelet-derived growth factor (PDGF) receptors. It is known that PDGF decreases interstitial fluid pressure. This suggests that the targeting of this molecule may lead to edema by blocking the signaling pathway between the dermal dendrocyte and the PDGF cytokine.

**Conclusion**

We believe that it is important to report this unusual adverse event and to understand its physiopathology to attempt to manage this complication without modifying the chemotherapeutic regimen.

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**Conflicts of Interest**
There are no conflicts of interest.

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