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Case Report

# Unusual Cutaneous reactions to Pemetrexed in a Patient with Metastatic non-small cell Lung Cancer

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**ABSTRACT**
Pemetrexed, a drug used in lung cancer and pleural mesotheliomas is mainly associated with hematological toxicities. Cutaneous toxicities, although well known are rare. This is a case of a metastatic adenocarcinoma lung with recurrent and localised skin lesions following each cycle of pemetrexed, which is the first report of its kind.

**Key words:** Lung cancer, Pemetrexed, Cutaneous toxicity, Localised, Recurrent, Rare.

**Key Messages:**
Pemetrexed, an antifolate drug is most commonly associated with hematological toxicities, and rarely with cutaneous toxicities. This is a case of a patient with metastatic non-small cell lung cancer who presented with recurrent, localized skin lesions at various sites in the body approximately 2 weeks after each cycle of pemetrexed.

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## INTRODUCTION

Pemetrexed is an antifolate drug recommended as a therapeutic agent in non-small cell lung cancer and pleural mesothelioma. Although its hematological toxicities are the anticipated dose limiting toxicities, cutaneous reactions do occur rarely. We report a set of unusual cutaneous reactions in a patient with metastatic adenocarcinoma of the lung who received pemetrexed in combination with carboplatin. The cutaneous reaction reported here is the first of its kind.

## CASE HISTORY

A 55 year old male, chronic smoker and hypertensive was referred to our hospital with complaints of diffuse chest pain and cough with whitish expectoration for a duration of one and a half months. He also had experienced weight loss which was not quantifiable. His physical examination revealed diminished breath sounds in the left hemithorax. The CT thorax revealed a lesion in his left lower lobe, which extended to involve the pleura and also encased the lower lobe bronchus. It also revealed metastatic nodules in the lingular lobe and the lower lobe with pretracheal and precarinal lymph nodes. Ultrasound guided Fine needle aspiration (FNA) of the lung lesion revealed a poorly differentiated adenocarcinoma. His investigations showed a normal haemogram, comprehensive metabolic panel included unremarkable renal function and liver function tests, normal electrolytes and negative viral markers. Metastatic work up showed a normal imaging of the abdomen, with evidence of multiple skeletal secondaries. His EGFR status was wild type. He was hence diagnosed as a case of metastatic adenocarcinoma of the left lung and started on combination chemotherapy with parenteral Pemetrexed (500 mg/m$^2$) and Carboplatin (AUC-5), on a 3 weekly basis along with monthly bisphosphonates.

Following the 1$^{st}$ course of chemotherapy (day 17), he developed a single pus filled bulla, measuring about 2.5×5 cm in the suprapubic region associated with purulent discharge. He had no associated systemic symptoms. He was treated with antibiotics, the bullous lesion subsided in 4 days and he received the second cycle of combination chemotherapy. On day 19 of the 2$^{nd}$ cycle, he presented to the outpatient clinic with complaints of painful swelling and redness of his nose in association with purulent nasal discharge from both his nostrils. Examination showed swelling and florid pustules over the exterior of his nose over a background of erythema. There was associated tenderness, but no constitutional symptoms. Pus culture of the nasal discharge grew Methicillin resistant *Staphyloccus aureus*. He was treated with antibiotics for 6 days, and was administered the 3$^{rd}$ course of chemotherapy once the acute episode subsided. He developed a single tender papule in the pubic region following the 3$^{rd}$ cycle on day 20, which was not associated with purulent discharge as the previous two episodes. His investigations- haemogram, renal and liver function tests, blood cultures showed no evidence of a systemic infection during the three episodes. The reassess-

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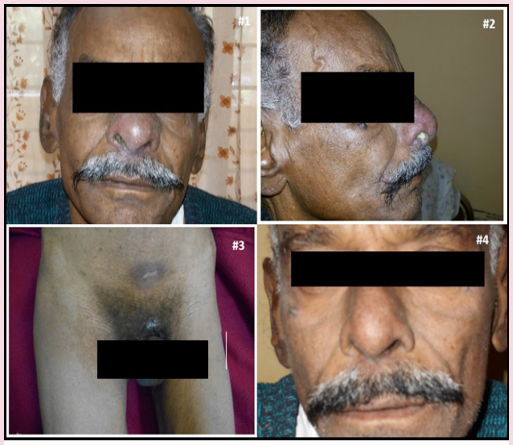


**Figure 1:** #1. & #2: Picture depicting a swollen nose with an erythematous pustular rash and purulent discharge from the right nostril, which developed following the 2nd cycle. #3: A healed scar in the suprapubic area which is the remnant of the pustule that appeared after the 1st cycle, and the papule in the pubic area developed following the 3rd cycle of pemetrexed. #4: Picture showing that the swelling and the lesions over the nose have subsided. This picture was taken during admission for the 4th cycle.

ment of the disease status at the end of 3 cycles showed progressive disease with appearance of new lesions in the body of the 11th thoracic vertebra and a nodule in the anterior segment of the left lower lobe with a static primary. The treatment regimen was changed to parenteral docetaxel.

## DISCUSSION

Pemetrexed, an antifolate used in non-small cell lung cancer and pleural mesothelioma, is associated principally with haematological toxicities. It is also rarely seen to cause cutaneous reactions, especially a rash (70–90% of patients who have not received corticosteroids, compared to in 14–50% of patients who have received corticosteroids). [1] Cutaneous toxicity of all grades has been observed in up to 14%, and grade 3 or 4 toxicities in 0.8–1.3% of cases.[2] The reported cutaneous adverse reactions include–alopecias( 17% grade 1, 2% grade 2),[3] cutaneous vasculitis, acute generalized erythematous pustulosis (AGEP), pityriasis lichenoides,[4] Steven Johnson syndrome (SJS)( 2 cases),[5] radiation recall dermatitis (3 cases reported),[6] and hyperpigmention of the palms and soles(<1%).[7] These reactions are benign, self-limiting events except for SJS which is life-threatening. Most of the cutaneous reactions are usually seen within the first few days of administration, however AGEP has been found to manifest after a latent period of 1–2 weeks.[8] AGEP is a rare self- limiting, drug–induced reaction with its differential diagnosis being subcorneal pustular dermatosis, pustular vasculitis, drug hypersensitivity syndrome and Stevens Johnsonsyndrome/toxic epidermal necrolysis.[8] The cutaneous reaction observed in our case was consistently after the 2nd week of each chemotherapy cycle, similar to how AGEP is seen to manifest. This probably is a localized, drug specific, adverse reaction to pemetrexed. As cutaneous reactions to carboplatin have not been documented earlier in literature, pemetrexed is most likely to be the causative agent for the above seen cutaneous manifestions. The pathogenesis of the cutaneous adverse effects are postulated to be a direct cytotoxic effect of the drug, however AGEP is thought to be T-cell mediated.[7] As the reactions in our patient developed more than a fortnight after pemetrexed administration, this is unlikely to be a direct cytotoxic effect and probably a T-cell mediated reaction similar to AGEP. Our patient received antibiotics on an empirical basis for a probable cutaneous infection, however since there were repeated episodes of isolated cutaneous manifestations, sparing all other organ systems and since there was a temporal relation of these manifestations to the administration of the drug, these episodes are more likely to be a drug specific side effect rather than recurrent community acquired infectious events. The stapylococcal organism isolated from the pus discharge was possibly a secondary bacterial infection.

## CONCLUSION

Cutaneous reactions to drugs such as pemetrexed although rare, seem to be of varied spectrum. Constant vigilance is required to differentiate milder reactions from more severe ones which would require discontinuation of the drug and that close monitoring is required to differentiate these from recurrent infections which would delay timely administration of the drug.

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## CONFLICT OF INTEREST

Nill.

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