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Year: 2013

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DOI: <https://doi.org/10.1016/j.lungcan.2013.02.019>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-76924>

Journal Article

Accepted Version

Originally published at:

Buchinger, Katharina; Stahel, Rolf; Niggemeier, Verena; Gubler, Christoph; Franzen, Daniel (2013). Pemetrexed-induced neutropenic enteritis and severe cutaneous hyperpigmentation in a patient with malignant pleural mesothelioma. *Lung Cancer*, 80(3):347-349.

DOI: <https://doi.org/10.1016/j.lungcan.2013.02.019>

**Pemetrexed-induced neutropenic enteritis and severe cutaneous hyperpigmentation in a patient with malignant pleural mesothelioma**

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## **Abstract**

Neutropenic enteritis (NE) or enterocolitis (NEC) is a rare, but potentially life-threatening side effect of neutropenia-inducing chemotherapy agents. Generally, its occurrence is attributed to leukaemia-associated chemotherapies. Two cases of NE have been reported after the appliance of pemetrexed for treatment of non-small cell lung cancers. To our knowledge, NE has never been reported due to treatment with pemetrexed for malignant pleural mesothelioma (MPM). We present a case of MPM in a 77-year-old male suffering from severe NE one week after the seventeenth cycle of pemetrexed in the course of maintenance therapy for MPM, which could be treated successfully with antibiotic coverage and supportive measures. Concomitantly the patient showed a severe hyperpigmentation of his entire integument sparing the palms of both hands and the soles of his feet. After exclusion of alternative causes of skin hyperpigmentation, a pemetrexed-induced cutaneous hyperpigmentation was assumed according to two previous case reports. A combination of both pemetrexed-induced side effects in one patient has not been reported to date.

## **Key words:**

Malignant pleural mesothelioma, pemetrexed, neutropenic enteritis, hyperpigmentation, lung cancer

## **Introduction**

Malignant mesothelioma is a highly malignant neoplasm related to asbestos-exposure, which develops from transformed cells originating in the mesothelium. The most common anatomical site of its manifestation is the pleura (malignant pleural mesothelioma, MPM), peritoneum, pericardium, or tunica vaginalis. Pemetrexed is an antifolate agent approved in 2004 for first-line chemotherapy of malignant mesothelioma in combination with carboplatin [1]. Furthermore, it has been approved as single-substance therapy for second line treatment of mesothelioma [2]. Several studies have shown a better safety profile and less gastrointestinal side effects of pemetrexed compared to other regimes in the treatment of non-small cell lung cancer (NSCLC) [3]. However, two cases of severe neutropenic enterocolitis (NEC) have been reported after the treatment with pemetrexed during treatment of NSCLC [4,5]. The incidence of NEC is unknown, but its occurrence is mainly attributed to neutropenia-inducing chemotherapies for acute leukaemias with a reported incidence of around 5% [6].

Here, we present the first case of a severe neutropenic enteritis (NE) in a patient receiving pemetrexed for maintenance therapy against MPM, who concomitantly showed a remarkable, diffuse cutaneous hyperpigmentation, which was previously reported in two cases only in association with pemetrexed [7,8].

## **Case Report**

A 77-year-old, never smoking, Caucasian man (height 179 cm, weight 71 kg, body surface area 1.89 m<sup>2</sup>) with stage III MPM (cT3, N0, M0) was admitted to the emergency department because of severe, diffuse abdominal pain with normal bowel movements, weight loss, and mild fever

beginning one week after the seventeenth administration of pemetrexed in the course of maintenance chemotherapy. The dose given was slightly reduced to about 420 mg/m<sup>2</sup>, since the kidney function was moderately impaired at that time (glomerular filtration rate 49 ml/min, serum creatinine 122 µmol/l, serum urea 8.9 mmol/l). The diagnosis of MPM was confirmed 23 months previous to the current presentation. The patient was initially treated with three cycles of a first-line chemotherapy including carboplatin (225 mg/m<sup>2</sup>) and pemetrexed (500 mg/m<sup>2</sup>) every four weeks. Thereafter, he was found in partial remission, and maintenance single-substance therapy with pemetrexed was introduced leading to stabilization of tumor growth. His further past medical history revealed coronary artery bypass graft surgery 10 years, and mitral valve repair 6 months prior to the event. Moreover, he suffered from intermittent atrial fibrillation and stage II chronic kidney failure. Medication on admission was phenprocoumon, acetylsalicylate, amiodarone, ramipril, torasemide, esomeprazole, potassium chloride, folic acid and cholecalciferol. Because of his recent abdominal pain, the patient additionally took paracetamol and butylscopolamine.

At presentation, the patient was normotensive and normocardic. The body temperature was 37.1° Celsius. The patient's entire integument showed severe, diffuse hyperpigmentation sparing only the palms of his hands and the soles of his feet. The auscultation of heart, lungs and the abdomen was unrevealing. The abdomen was soft, but diffusely tender to percussion and palpation. Laboratory studies were only remarkable for moderate anaemia (haemoglobin 83 g/l) and elevated inflammatory markers (C-reactive protein 53 mg/l, erythrocytes sedimentation rate 100 mm/h), but leukocytes within the normal range

A contrast enhanced computed tomography (CT) scan of the abdomen revealed segmental small bowel wall thickening (5 mm) without involvement of colon or caecum precluding ileus, bowel perforation, ischemia, (pseudomembranous or inflammatory) colitis, acute appendicitis, cholecystitis, or pancreatitis (figure 1) . Moreover, radiologic signs of peritoneal mesothelioma manifestation were not present. An empirical antibiotic therapy with metronidazole was initiated, because infectious enteritis was assumed, though there was no fever, no diarrhea and a normal white blood count. Three days after, the patient developed febrile neutropenia with a minimal neutrophiles count of 220/l, fever up to 38.6°C and worsened abdominal pain and new onset diarrhea. Thrombocytes decreased to 109000/l, and haemoglobin was unchanged.

Although there was no microbiologic evidence of an infection in the previously taken blood and stool specimen (including negative stool antigen testing for *Clostridium difficile* and negative serum cytomegalovirus PCR), the anti-infective treatment was expanded with piperacillin/tazobactam and fluconazole assuming neutropenic enteritis in order to prevent penetrating peritonitis. Moreover, bowel rest and total parenteral nutrition was initiated.

The following week, the patient's condition and his neutrophiles count (4630/l) improved considerably. A follow-up abdominal CT scan confirmed resolution of the bowel wall thickening. After a total of 43 days, the patient was transferred to a rehabilitative institution. The asymptomatic but severe hyperpigmentation of his entire skin was unchanged during hospitalization. The patient's former Caucasian complexion had been started to turn a dark brownish shade (*figure 2-3*) two months previous to the current presentation without being exposed to sun light or using self-tanning lotions. Haemochromatosis seemed unlikely, as ferritin and transferrin saturation were within normal ranges one year before. Moreover, adequate

increase of cortisol levels upon cosyntropin and a normal morning serum cortisol level excluded adrenal insufficiency. Also, other less frequent differential diagnoses of diffuse cutaneous hyperpigmentation could have been excluded by absent exposition to silver containing agents precluding systemic argyria. Considering pharmacological side effects due to his usual medications, only pemetrexed and amiodarone was a potential causative agent for dermal hyperpigmentation. However, amiodarone was introduced after the first observation of the patient's color-related skin alterations.

## **Discussion**

The pathogenesis of NE (or accordingly neutropenic enterocolitis, NEC) is poorly understood. The disease seems to be caused by the combined effect of chemotherapy-induced neutropenia and direct toxicity of chemotherapeutical agents against the intestinal mucosa [9]. Together with endotoxin-production, this mechanism enables intestinal bacteria to invade the bowel wall leading to ischemia, ulceration and necrosis [4]. This potentially life-threatening disorder is commonly seen following induction chemotherapy for leukaemia. Furthermore, it is occasionally observed after highly aggressive chemotherapies against solid tumors [5]. Two cases of NE or NEC have been reported after the appliance of pemetrexed in the treatment of NSCLC [4,10]. To date, only one case of fatal NEC has been reported after chemotherapy for MPM [11]. However the latter case occurred administering a chemotherapy agent other than pemetrexed. Our patient suffered from combination of severe NE and diffuse cutaneous hyperpigmentation during maintenance chemotherapy with pemetrexed, although his glomerular filtration rate was more than the lower limit of 45 ml/min, and, however, the given dose had been reduced to 723 mg/m<sup>2</sup>. Current treatment recommendations for MPM do not include maintenance

therapy [12]. But pemetrexed was shown to be safe and generally well tolerated [4]. The pemetrexed-associated colitis rate was 0.6% in the clinical trial database, and gastrointestinal side effects are reported to be less than 1% [3,4]. Two months previous to the patient's presentation, he noticed a progressive hyperpigmentation of his entire integument sparing the palms of both hands and the soles of his feet. He denied any sun exposure or the use of self-tanning lotions, and alternative differential diagnoses of cutaneous hyperpigmentation including haemochromatosis, adrenal insufficiency, and systemic argyria had been excluded. According to two previous case reports, a pemetrexed-induced cutaneous hyperpigmentation was therefore assumed [7,8]. The reported patients developed hyperpigmentation shortly after administration of pemetrexed. In the first case, the patient showed asymptomatic hyperpigmentation of his palms and soles after the second cycle of pemetrexed [7]. The second report describes two patients, who developed diffuse hyperpigmentation of the upper part of the body resolving after cessation of pemetrexed [8]. But, the dose and number of pemetrexed administrations are not mentioned in these patients. Anyway, cutaneous adverse effects are supposed to correlate directly with the administered dose and number of pemetrexed cycles, respectively [13]. Thus, the prolonged appliance of pemetrexed could play a causative role in the development of hyperpigmentation [8], but also in the pathogenesis of NE(C), irrespective of glomerular filtration rate as seen in the present case. The pathogenesis of pemetrexed-induced hyperpigmentation of the skin yet remains unclear. Anyway, pemetrexed is associated with several cutaneous side effects described elsewhere [8].

## **Conclusion**

The increasing use of pemetrexed and other neutropenia inducing chemotherapies, and the thereby achieved improved survival rates are likely to cause higher rates of severe or potentially life-threatening adverse effects. Abdominal pain and bowel wall thickening in CT scans in patients being treated with pemetrexed should be an alarm signal for clinicians to consider possible NE(C). Aggressive and multidisciplinary approach should be initiated rapidly to prevent fatal outcomes [14]. To date, pemetrexed-induced cutaneous hyperpigmentation may be underestimated. However, both side effects should be considered after exclusion of alternative causes, particularly when pemetrexed is administered for a prolonged period of time, even in adequate dosage adapted to the current kidney function.

#### **Conflict of interest statement**

There is no conflict of interest to declare.

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