Case Report

Pemetrexed-induced mucocutaneous hyperpigmentation in an atypical case of malignant pleural mesothelioma

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ABSTRACT

Development of cutaneous adverse effects secondary to pemetrexed is an uncommon occurrence. Here, we present an unusual case of a 22-year-old young male who developed malignant pleural mesothelioma without having any known risk factors. When started on first-line chemotherapy with pemetrexed and cisplatin, he developed hyperpigmented macular rashes over the palms, soles, and the dorsum of the tongue. Although, the better outcome has been reported previously in young patients in terms of response to chemotherapy, unfortunately, our patient had a rapid progression and poor outcome. Our case did not have a favorable course though and rapidly succumbed.

Key words: Adverse reactions, Lung cancer, Pharmacology, Therapeutics

Malignant pleural mesothelioma is a rare malignancy arising from the mesothelial cells lining the pleural cavity. Individuals with prolonged inhalational asbestos exposure as in ship-building, plumbing, pipe fitting, etc., are at risk of developing mesothelioma, lifetime risk being as high as 8–13% [1]. As it usually takes decades to develop, it usually occurs among middle-aged and elderly people. Very rarely, it presents in younger age groups defying the classical presentation. It has an aggressive course and poor outcome. Pemetrexed is a commonly used chemotherapeutic agent in lung cancers. Its side effect profile includes hematological and non-hematological side effects. Hyperpigmentation in the absence of other cutaneous lesions is uncommon and only a few cases have been reported so far [2-4].

CASE REPORT

A 22-year-old Indian male engineering college student, presented to us with a complaint of severe respiratory distress which had started as dyspnea on exertion but gradually progressed over a period of 2 months to become severe enough at rest. The patient also complained of left-sided chest pain which was moderate and dull-aching type, non-radiating, and relieved by analgesic (Ibugesic). He had an intermittent high-grade fever, not associated with chills/rigors/muscular pain, and relieved by taking antipyretics (paracetamol). He also complained of weakness and weight loss of about 5 kg in the past month before hospitalization. He had been receiving anti-tubercular therapy (Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide) for 1 week on a clinical basis. There was no history of tuberculosis or any other chronic disease. The patient had no history of drug allergy. There was no family history of any malignancy, tuberculosis, or any other chronic disease.

At the time of admission, the patient was afebrile, had tachypnea (respiratory rate 30/min), tachycardia (heart rate 122/min), and normal blood pressure (110/60 mmHg) with SpO_2 of 85% with room air. There was no neck vein engorgement or pedal edema. On palpation, the trachea was deviated toward the right and on percussion, the entire left lung field was stony dull. Cardiac dullness was masked. On auscultation, air entry was grossly decreased on the left side.

Blood investigations were within normal limits and the pleural fluid report was as follows: Turbid red in color, exudative, and Adenosine Deaminase (ADA) of 14.9 U/L. Acid-fast bacilli (AFB) smear, Cartridge-based Nucleic acid amplification test (CBNAAT) for Mycobacterium and Malignant cytology (three samples) results were negative. The chest radiograph showed massive effusion with mediastinal shift to the right. Ultrasonography whole abdomen showed left-sided pleural effusion. Contrast-enhanced computerized tomography (CECT)

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of the thorax revealed a circumferential beaded growth suspicious of malignancy (Fig. 1).

On thoracoscopy, 1.5 L of hemorrhagic pleural fluid was aspirated and both the pleural surfaces were seen to be studded with reddish nodular growth. A biopsy was taken and ICD was removed when there was no output for three days. Histopathology and immunohistochemistry revealed malignant mesothelioma (Fig. 2). On retro-inspection and review of history, there was no history of exposure to asbestos, stay in an industrial area, talc exposure, or smoke or any known risk factor.

The patient received two cycles of chemotherapy (Pemetrexed plus Cisplatin) from our center. When he arrived for the third cycle, he had developed a brown color macular rash over the dorsum of the tongue and palms and soles (Fig. 3). Dermatology opinion was sought and the rash was attributed to pemetrexed. The patient had developed a persistent high-grade fever (~104–105°F) with severe dyspnea. The total leukocyte count (TLC) was 50,000/mm^3 (Neutrophils 80%, lymphocytes 18%, and eosinophils 2%) despite the patient being on broad-spectrum antibiotics. The patient deteriorated rapidly and expired on the second day of admission despite all measures.

DISCUSSION

Malignant pleural mesothelioma is usually considered a disease of the elderly with a median age of 75 years as prolonged exposure to asbestos is required for malignant transformation of mesothelial cells [5]. Occupations such as plumbing, pipe-fitting, steam fitting, mechanical engineering, and industries such as ship and boat building have the highest risk of developing mesothelioma as they cause exposure to asbestos [6]. Our case was an exception as the patient was a student who had just joined engineering college and resided in a non-industrial area. Very rarely, it occurs among patients who are young and are not related to asbestos exposure [7,8]. In 1981, Brenner *et al*. reported seven cases of mesothelioma, six of which were pleural and one peritoneal which had no asbestos exposure [9]. Germline BAP mutations have also been implicated in the etiology of mesothelioma [10,11]; however, our patient had no family history suggestive of the same.

Pemetrexed is an anti-folate anticancer agent which inhibits thymidylate synthetase thus inhibiting the synthesis of nucleic acids. It causes cell cycle arrest in S-phase. The same cytotoxic mechanism leads to cutaneous and hematological adverse effects of the drug. Cutaneous toxicity of pemetrexed includes a wide spectrum ranging from alopecia, urticarial vasculitis, exanthematous pustulosis, and radiation recall dermatitis to toxic epidermal necrolysis [4,12].

Generalized hyperpigmentation was reported in 2009 by Tolayamat *et al*. [13]. Hyperpigmentation of palms and soles was reported for the first time by Schallier *et al*. in 2011 wherein the patient developed brownish hyperpigmentation after two cycles of pemetrexed as we found in our case [2]. However, the rash was reversible on discontinuation of the drug in their case while reversibility could not be documented in our case as he

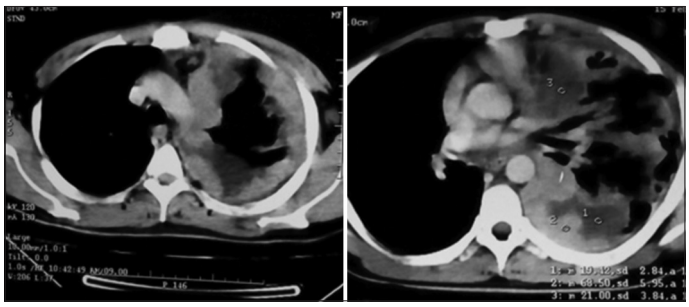

Figure 1: Axial section of contrast-enhanced computed tomography of thorax showing circumferential beaded growth

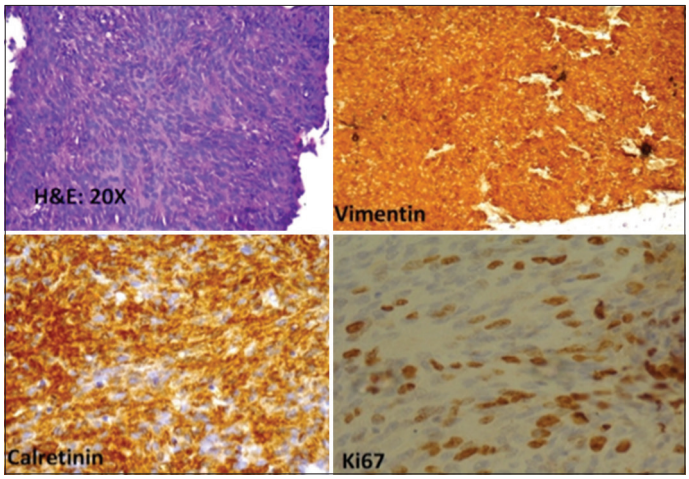

Figure 2: Section showing biopsy tissue enclosing a neoplasm with spindled cells displaying cellular mitosis (H and E ×20). On further immunohistochemistry the tumor cells expressed vimentin and cytokeratin calretinin. Ki67 was 20%

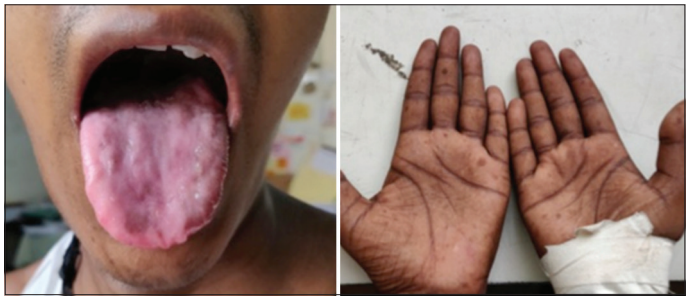

Figure 3: Dorsum surface of tongue and palmar aspect of hands showing hyperpigmented macular

deteriorated rapidly and succumbed when he came for the third cycle. In 2013, Buchinger *et al*. reported hyperpigmentation in a case of malignant pleural mesothelioma treated with pemetrexed. In their case, however, palms and soles were spared [4]. The previously better outcome has been reported among younger patients [14], perhaps due to different pathophysiology. Our case did not have a favorable course though and rapidly succumbed.

Unilateral pleural effusion in a young male with a 2-months history of dyspnea, weight loss, and fever in an endemic country like India usually leads to tubercular etiology. However, the massive nature of effusion, hemorrhagic color, and low ADA did not favor the diagnosis. A negative Mantoux test further raised suspicion of a different etiology. CECT thorax demonstrated circumferential

beaded pleura-based growth which was highly suspicious of malignancy may be mesothelioma. However, there was no history of asbestos exposure or family history of malignancy. Later on, histopathology confirmed the diagnosis. The brown rash that the patient developed was attributed to pemetrexed after consultation with dermatology opinion. Oculocutaneous melanoma can be seen in cases of mesothelioma due to BAP-1 mutation; however, our patient developed the rash only after receiving two cycles of pemetrexed. Workup for BAP-1 mutation was planned but the patient was in low general condition and expired soon thereafter; therefore, further investigations could not be done.

CONCLUSION

Although considered to be a malignancy of the elderly, malignant mesothelioma may rarely present in the younger age group. While prolonged asbestos exposure is associated with the development of malignant pleural mesothelioma, in a younger subgroup of patients, it may develop in absence of any such exposure. This certainly requires further studies to ascertain the different pathogenic mechanisms among the young. Although, the better outcome has been reported previously in young patients in terms of response to chemotherapy, unfortunately, our patient had a rapid progression and poor outcome.

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