

# Novel anticancers and dermatological adversities: old rivals but new challenges

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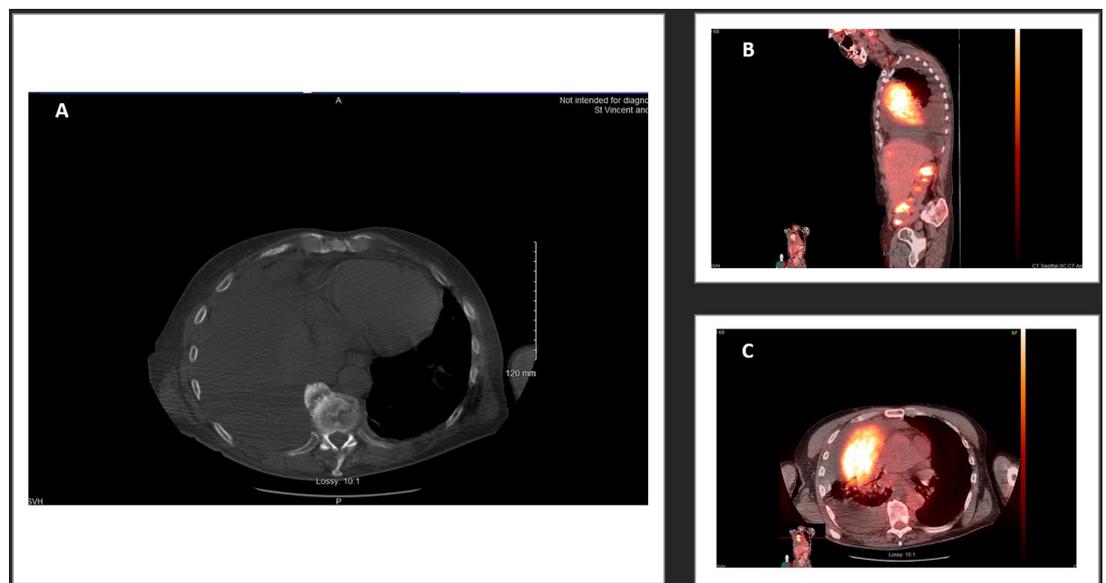
## DESCRIPTION

A 68-year-old ex-smoker with 5-year history of controlled hypertension on once daily dose of losartan 25 mg presented with breathlessness of 2 months duration. X-ray showed right-sided pleural effusion. CT chest also confirmed huge lung mass with moderate right pleural effusion (figure 1A). The pleural fluid cytology was positive for malignant cells. PET scan showed homogeneous hypermetabolism of conglomerate mass/adenopathy with maximum standardized uptake value of 6.8 (figure 1B,C). Diagnosis of stage IV lung adenocarcinoma with malignant pleural effusion was made. He was started treatment with a 3-weekly cycle of pemetrexed (500 mg/m<sup>2</sup> intravenous once on day 1) and pembrolizumab (200 mg intravenous on day 1). At the end of third cycle, he noticed itchy rashes all over his body. It was initially on his back and then spread downwards involving his trunk, arms and legs. He denied any history of fever or chills. Skin examination showed diffuse ill-defined erythematous maculopapular rash over the back, chest and abdomen (figure 2A,B). At places few nodules were present. Diffuse erythematous to violaceous patch was present over the lower one-third of bilateral lower limbs (figure 2C). Based on the history and clinical features, a probable diagnosis of maculopapular rash secondary to anticancer drugs was made. We offered skin biopsy for further evaluation, but the patient refused. Further chemotherapy

was withheld, and he was started on oral prednisolone 0.5 mg/kg once daily dose and syrup diphenhydramine HCl (25 mg every 8 hourly). Clinical examination after 2 weeks showed fading of skin lesions. Patient opted out of any more anticancer treatment and enrolled for palliative care. Inability to obtain a skin biopsy limited the ability to histologically differentiate and identify the responsible drug in our case.

Patients with stage IV disease who are treated with immunotherapy can have an average overall survival anywhere from 18 to 24 months. Our patient received two newer anticancer drugs which were the probable cause of skin rash. Immune checkpoint inhibitors (eg, pembrolizumab) targeting programmed death ligand-1 (PD-1) on tumour cells are recently used in the treatment of several cancers. As pembrolizumab is an immune modulator, it can topple the immune homeostasis against body's own cells leading to immune-related adverse effects like pneumonitis, colitis, hepatitis, hypothyroidism, hyperthyroidism, nephritis, etc.<sup>1</sup>

Similarly, pemetrexed is a novel anti-folate antimetabolite agent that is also rarely known to cause skin rashes. Manufacturers of pemetrexed have recommended premedication with 5–7 days of folic acid and 3 days with dexamethasone 4 mg twice daily on the day before, the day of and the day after infusion. Despite following premedication scheme, our patient still experienced skin rashes.



**Figure 1** (A) Complete collapse of the right upper and right middle lobes. Mass effect from underlying mass, which is inseparable from the mediastinum/right hilum and adjacent collapsed lung. (B) Sagittal and (C) axial. PET showing homogeneous hypermetabolism of the collapsed lobes with maximum SUV 6.8.



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**Figure 2** (A,B) Skin examination showed diffuse ill-defined erythematous maculopapular rash over the back, chest and abdomen. (C) Diffuse erythematous to violaceous patch was present over the lower third of lower limbs.

Immune-mediated skin rashes can range from simple dry skin to fatal Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) complex. Depending on the severity and grade of skin reactions, immune therapies can be withheld for a while or discontinued permanently. It is also important to adequately evaluate and rule out other possible aetiologies of skin lesions like infection, tumour infiltration, etc.

In a study including 88 patients of advanced melanoma on pembrolizumab, the most common AEs were cutaneous.<sup>1</sup> Similarly, cutaneous AEs were reported in 40%–60% of patients on pembrolizumab in other studies as well. Most common cutaneous AEs identified were maculopapular rash, followed by pruritus and hypopigmentation. Other cutaneous manifestations that have been reported are vesicles, blisters and psoriasiform lesions.<sup>1,2</sup> Mucosal involvement in the form of necrotic ulcerations of lip, and erosive oral mucositis, blepharconjunctivitis have also been reported.<sup>2</sup> Recently, Kunimasa *et al* reported interesting case of pembrolizumab-related skin rash. They found extensive CD8 (+) PD-1 (+) T-cell infiltration in the immunofluorescence analysis of the skin biopsy.<sup>3</sup> They proposed revival of immune cells as the cause of skin rash during anti-PD1 therapy. Recent studies have not shown any evidence of worst outcome among patients developing cutaneous AEs as well. Most patients with cutaneous AEs respond well to topical steroids like betamethasone.

Similarly, pemetrexed can cause a variety of cutaneous AEs like alopecias, TEN, urticarial vasculitis, exanthematous pustulosis, radiation recall dermatitis, etc. Likely mechanism may be due to (1) direct cytotoxic effect due to arrest of cell cycle 'S phase'

leading to cell necrosis or (2) indirect immune reaction. Piérard *et al* suggested that a high Ki67 index could point towards cell cycle blockade versus calprotectin (MAC 387) immunopositivity of keratinocytes as a soft indicator of immunological perturbation.<sup>4</sup> Usui *et al* in their study concluded that mandatory dexamethasone as premedication before pemetrexed-based therapy reduced the frequency of grade  $\geq 2$  skin rash by at least 10%.<sup>5</sup> In past, many anti-cancer drugs are reported to be associated with dermatological adverse effects<sup>(6,7)</sup>. More studies are needed to know the exact pathophysiology behind the cutaneous AEs and for possible remedies.

### Learning points

- ▶ Knowledge of cutaneous adverse events would prevent unnecessary investigations and expedite the treatment.
- ▶ Premedication before immunotherapies is advisable but may not avert immune-related adverse effects in every case.
- ▶ Thorough examination of patient in every visit is mandatory before prescribing the next cycle of chemoregimen.

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