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LETTER TO THE EDITOR

Scleroderma induced by paclitaxel

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To the Editor,

Paclitaxel is a standard treatment of a variety of solid tumours. It binds to microtubules at the tubulin ß subunit causing an increase in microtubule polymerisation. The result is inhibition of the normal dynamic reorganisation of the microtubule network essential for normal cell function. As a consequence a miotic arrest is induced eventually leading to apoptosis [1].

Paclitaxel is mainly excreted in the stool via the enterohepatic circulation over approximately five days as parent compound and metabolites. Premedication with steroids is necessary to prevent taxane related hypersensitivity. Nevertheless major hypersensitivity reactions occur in 3% despite prophylaxis. Side effects include bone marrow suppression, pulmonary toxicity, nail disorders and skin toxicity [2].

Scleroderma is an autoimmune systemic connective tissue disease which is characteristic by blood vessel changes and fibrosis of the skin. The fibrosis can appear in any organ. The aetiology and pathogenesis of scleroderma is unknown, however the most important genetic predisposition is female gender [3].

We report a case of possible paclitaxel induced scleroderma in a patient with ovarian/peritoneal cancer and present a review of related literature.

Case report

A 52-year-old woman was diagnosed with ovarian/peritoneal cancer FIGO stage IIIc. Biopsy showed low differentiated adenocarcinoma with an immunohistochemistry profile consistent with primary ovarian or peritoneal cancer.

She started primary chemotherapy three times weekly with paclitaxel 305 mg i.v. (175 mg/m^2) and carboplatin 525 mg i.v. Area Under the Curve, AUC 5. After the second cycle an allergic reaction with flushing and oppression was observed and she was treated with 100 mg of prednisone 12 hours prior to cycle three. She received a total number of six cycles before having delayed debulking surgery.

She underwent a bilateral salpingooophorectomy with supravaginal hysterectomy, peritoneal excision and appendectomy. A combination of fetanyl, thiopental, rocuronium, propofol and alfentanil was used as anaesthetics. She was referred for additional three cycles because of residual disease.

A month after surgery she complained of paraesthesiae of her lower extremities and difficulty with motor function, grade 2 toxicity according to the Common Toxicity Criteria (CTC). The paclitaxel dose was reduced with 25% in the seventh cycle, nevertheless her symptoms deteriorated.

On cycle eight day eight she experienced grade 2 dyspnoea and the ninth course was cancelled.

Nine months after the last cycle of chemotherapy she had developed oedema of the face, neck and feet. Gabapentin had been started for neuropathic pain but stopping it did not relieve the oedema.

Fibrosis proximal of the metacarpophalangeal joint and in the face, Raynaud´s phenomenon, athralgia, and subsequently microstomia and dyspnoea were found on clinical examination.

Anti nuclear antibodies, double stranded DNA, specific antibodies against SSA/SSB and ScL70 were negative. X-ray of the thorax and oesophagus and nail fold capillaroscopy were normal. Pulmonary function tests showed slightly reduced DLCO of 53% indicating a vasculopathy of the lungs but with no signs of pulmonary hypertension.

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Table I. Taxane induced scleroderma: A review of the literature.

Case	Drug	Dose, mg/m^2	Time lag to symptoms, months	Autoantibodies present
Battafarano et al.	Docetaxel	100	8	Negative
Battafarano et al.	Docetaxel	100	5	Negative
Battafarano et al.*	Docetaxel	100	3	Negative
Tamihiro et al.	Paclitaxel	Not available	10	Positive
Eisenbeis et al.	Paclitaxel	Not available	6	Positive
Farrant et al.	Paclitaxel	Not available	60	Negative
De Angelis et al.	Paclitaxel	175	8	Negative
Kupfer et al.	Paclitaxel	175	7	Negative
Cleveland et al.	Docetaxel	125	21	Negative
Hasset et al.	Docetaxel	100	7	ANA positive 1/2560 with a speckled pattern
Läuchli et al.	Paclitaxel	175	6	Negative
Akrekar et al.	Paclitaxel	Not available	3	ANA positive with a speckled pattern
Vitfell/Jensen et al.	Paclitaxel	175	6	Negative

*This patient had thickening of the skin, but did not have a biopsy that confirmed the diagnosis.

Skin biopsies taken from the abdomen demonstrated increased thickness of dermis composed of broad and sclerotic collagen bundles extending to the underlying subcutis. There were vascular changes with thickening of small blood vessels wall and a light inflammatory perivascular infiltrate composed of lymphocytes. These findings were consistent with the diagnosis of scleroderma.

Treatment consisted of Ultraviolet A light, nifedipine, esomeprazole and methotrexate.

At the end of this reporting she was still suffering from severe fibrosis of the skin, but with no clinical or radiological signs of cancer and a normal CA 125.

Discussion

A literature search revealed 10 studies reporting a total of 12 cases of scleroderma following treatment with taxanes (Table I). Other studies have demonstrated an increased risk of lung- and breast cancer for patients with scleroderma [4,5] and cases with scleroderma and ovarian cancer have also been reported [6].

In our case the patient had cancer prior to the scleroderma and it is therefore unlikely that scleroderma had caused the cancer.

The symptoms started six months after receiving the paclitaxel treatment and one month after surgery. During surgery one of the most frequently used combinations of anesthetics, analgesics and muscular relaxants were used and none of these drugs are known to cause scleroderma. A literature search did not reveal any cases of scleroderma combined with each drug, neither separately nor in combination.

In addition to the scleroderma, the patient had Raynauds´s phenomenon, which is a known adverse effect for carboplatin but to our knowledge it has never been found to cause scleroderma [7].

Since the patient had no anti-nuclear antibodies, it is unlikely that this case is an autoimmune reaction. In the 12 other cases eight had negative ANA, two had low ANA with speckled pattern but no specific auto-antigens and two had positive ANA but negative anti-ScL70 [8–11].

It is also unlikely that the case represents a paraneoplastic phenomenon because the first symptoms of scleroderma occurred after six cycles of chemotherapy. Had it been a para-neoplastic phenomenon one would have expected the symptoms to decrease during treatment but instead they deteriorated despite remission of the cancer.

In summary it seems that paclitaxel was the most likely cause of the scleroderma diagnosed in this patient. That is due to the mean interval between start of taxenes and diagnosis of scleroderma was seven and a half months in the prior 12 cases and in our case it was six months.

Paclitaxel is an important drug in the treatment of many cancers and its use is increasing. Clinicians should be aware of this rare but highly disabling adverse effect.

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