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Unintended benefits of immunosupression on autoimmune disease due to chemoradiation therapy for head and neck cancer

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Abstract The immune system is an important factor in the host's defenses against cancer. Immunosupression by radiation and/or chemotherapy is often associated with systemic and hematologic complications, opportunistic infections, and the development of malignancies, but immunosupression can also have beneficial effects, which are sometimes incidental. We report 2 patients with autoimmune diseases where immunosupression had beneficial effects. The first case is about a patient with carcinoma of the tonsil, with severe rheumatoid arthritis, who was treated with chemoradiation, which resulted in remission of his arthritis. The second case is about a patient with severe atopic eczema who was on long-term treatment with psoralen and ultraviolet A radiation and azathioprine; the patient developed metastatic carcinoma of the lip, which was treated with surgery and radiation that resulted in complete remission of his eczema.

1. Case 1

A 67-year-old man was referred to the ear, nose, and throat (outpatient) department for vertigo.

On routine examination he was found to have a unilaterally enlarged left tonsil, and palpable left cervical nodes at levels I and II.

He underwent an excision biopsy of the tonsillar mass, fine needle aspiration cytology (FNAC) of the lymph nodes, and a direct laryngoscopy.

Histopathologic examination of the biopsy revealed a poorly differentiated squamous cell carcinoma (SCC), and FNAC revealed metastatic carcinoma. Direct laryngoscopy yielded normal results.

He had a significant medical history of hypertension, angina, and stroke. The patient had a 14-year history of seropositive erosive rheumatoid arthritis affecting his cervical spine, shoulders, wrists, knees, ankles, and distal interphalangeal joints. He had morning stiffness of 3 to 4 hours, and had severe restriction of movement in these joints, with associated myalgia and synovitis. He mobilized with 2 sticks and could barely walk 50 yards. He had been treated in the past with gold injections, sulfasalzine, and nonsteroidal anti-inflammatory drugs, and was on long-term methotrexate (7.5 mg weekly) and folic acid.

He had significant comorbidity and was not keen for radical surgery; therefore, it was decided to treat him with radiotherapy of 5500 cGy given as 26 fractions and concomitant chemotherapy. His methotrexate and folic acid were discontinued during chemoradiotherapy, and were not administered again, keeping in mind the risk of developing a second malignancy.

After 2 cycles of chemotherapy (carboplatin, 5-fluorouracil [5-FU], and folinic acid), he had significant remission of rheumatoid arthritis.

Before chemotherapy, his rheumatoid arthritis was so severe that he needed the support of 2 walking sticks, and could barely manage to walk 50 yards.

After chemotherapy, he was able to walk 200 yards unaided, without discomfort, and with much improved

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balance. His morning stiffness now only lasted from 30 to 40 minutes, and his joint movements particularly at the cervical spine were much improved with significant reduction of myalgia. The patient has been followed up (otolaryngology and rheumatology) in the past 3 years and has shown no signs of local or regional recurrence; his rheumatoid arthritis is well controlled and he is on nonsteroidal anti-inflammatory drugs on an as-required basis.

2. Case 2

Case 2 represents a 45-year-old patient, referred from Dermatology, with a painless, nonhealing ulcerated lesion of the lower lip.

The patient was under the care of dermatologists for the past 6 years for treatment of severe atopic eczema mainly involving the face and neck and the upper trunk. He had been treated with psoralen and ultraviolet A radiation (PUVA) (total of 268 cycles varying from 2 to 4 J for the past 2 years). He had also been treated with azathioprine (100–150 mg, bid) for the past 5 years, but had shown only a temporary limited response to the treatment.

On examination, he had a 1 × 0.5 cm ulcerated lesion on his left lower lip (near the vermilion border), with an indurated base. There was no clinical or radiologic evidence of metastases. He had a full-thickness wedge excision of that lesion. Histolopathology revealed a poorly differentiated SCC completely excised with a 5-mm margin, with no evidence of lymphatic or vascular invasion.

Four months later, he presented with an 8-week history of a left-sided neck lump. FNAC was consistent with metastatic SCC. A repeat computerized tomography scan revealed a 3-cm level I cervical neck node almost fused with the submandibular gland, and multiple left small cervical nodes at levels III and IV.

He subsequently underwent a left radical neck dissection. Histopathology revealed metastatic deposits in the submandiblar lymph node with extracapsular invasion and node involvement in the left neck levels III and IV. Postoperatively, he underwent radiation (4500 cGy) to the neck and mediastinum.

During the course of his surgery and radiation, treatment with azathioprine and PUVA was stopped. After radiation treatment, it was noted that his eczema had subsided.

Before he was diagnosed with metastatic lip cancer, the patient had recurrent pruritic exudative papular eruptions involving the neck creases, ear lobes, and face, and pruritic pustular eruptions on his upper chest associated with skin fissuring. Despite treatment with PUVA and azathioprine, control of his lesions and symptoms was only temporary and limited.

After completion of radiotherapy his eczema has been quiescent. The eruptions on his face, neck, and chest had dried up. There was residual dryness but his pruritis had significantly reduced. He was only kept on regular local emollients and occasional topical steroids.

He has been regularly followed up by dermatology and otolaryngology for the past 4 years; so far, the patient has shown no signs of local or regional recurrence of tumor and his eczema has remained well controlled on local emollients.

3. Discussion

3.1. Case 1

Disease-modifying antirheumatic drugs are widely used in the management of severe rheumatoid arthritis, and drugs such as methotrexate and azathioprine have been in use for a long time.

Bunch et al [1] described an anecdotal experience in treating patients with metastatic colorectal cancer, who coincidentally also had rheumatoid arthritis, with 5-FU and leucovorin that led to a drastic improvement in the patients' symptoms of rheumatoid arthritis. Jensen and Mejer [2] described an experience with a 71-year-old patient who had a 12-year history of severe rheumatoid arthritis treated in the past with Salazopyrin and methotrexate. He was treated with 2 cycles of chemotherapy for metastatic colonic cancer, which resulted in remission of his rheumatoid arthritis.

The patient described here received 2 cycles of chemoradiation in the form of carboplatin, 5-FU, and folinic acid, before which his long-term treatment with methotrexate and folic acid was discontinued.

The plausible explanation for this is that his arthritis was methotrexate-resistant and responded to 5-FU.

5-Fluorouracil inhibits thymidylate synthase and the formation of thymidine. Irreversible binding occurs in the presence of N5,N10-methylenetetrahydrofolate. N5,N10-methylenetetrahydorfolate is only synthesized in the presence of dihydrofolate reductase (DHFR) [3,4]. Methotrexate inhibits DHFR that converts folate to tertrahydrofolate. These active forms of folate are essential in purine and thymidine synthesis and by inhibiting the DHFR, the synthesis of purines and thymidine are interrupted, which interferes with the cell cycle [4]. Treatment with methotrexate often leads to the emergence of drug-resistant diseases that contain vastly elevated levels of the target enzyme, DHFR [5]. In cultured cells, overproduction of the enzyme usually results from specific amplification of a large DNA segment that includes the DHFR gene [5]. That way, the cell escapes interruption of the cell cycle in the presence of methotrexate. The patient probably had elevated levels of DHFR as a result previous methotrexate treatment, and therefore 5-FU inhibited thymidylate synthetase irreversibly.

The intention was to treat the head and neck malignancy, but the chemotherapy (immunosupression) also unintentionally resulted in the remission of symptoms of rheumatoid arthritis.

3.2. Case 2

Since the 1970s, PUVA has been an effective therapy used to treat skin disorders such as psoriasis and eczema. There have been many studies over the years that have documented the increase in the risk of cutaneous SCC in patients treated with PUVA.

Both European and US studies [6-9] have demonstrated that patients exposed to high doses of PUVA therapy have a significantly increased risk of SCC of the skin.

Psoralen and ultraviolet A radiation and Cancer Risk: The Swedish follow-up study 10 followed up more than 4000 patients treated with PUVA for more than 15 years, and inferred an increased risk of cutaneous SCC. (The relative risk of developing cutaneous SCC was determined as 5.6 for men and 3.6 for women.) There is also evidence of a dose-dependent increased risk of SCC in association with PUVA treatment [10,11].

Stern et al [6,7] analyzed data on 1183 patients with a first SCC by treatment duration and level of exposure to PUVA. The number of patients who developed SCC receiving more than 337 PUVA treatments were twice in number compared to the ones receiving less than 100 PUVA treatments.

Atopic eczema is widely treated with azathioprine in the UK [12].

The long-tem use of azathioprine has been well associated with the development of SCC [13,14]. Azathioprine disrupts the synthesis of DNA and RNA, causing effective immunosupression by interfering with lymphocyte proliferation [15].

Dalton et al [16] postulated that azathioprine and UV light have a synergistic effect on DNA causing a carcinogenic change, particularly in skin cancers. They studied the synergistic effects of azathioprine and UV light detected by sister chromatid exchange analysis. Azathioprine exerts its immunosuppresant effect via 1 of its metabolites, 6-thioguanine, which is subsequently incorporated into DNA. Incorporation of 6-thioguanine into DNA and its subsequent oxidation in situ by UV light is an obvious mechanism by which DNA damage can occur and carcinogenic change arise.

Radiation therapy for the treatment of benign dermatoses has been used in the past. Jansen [17] reported the use of Grenz rays (low-energy x-rays produced with a potential of less than 20 kV) therapy for select cases of eczematous conditions with good results. Superficial radiation therapy (x-rays with energies between 50 and 150 kV) has been used in the past for benign dermatoses.

Treatment of eczema refractory to other forms of treatment with megavoltage radiotherapy has been described before [18], but concerns over carcinogenic effect of radiation for benign disease have prompted a reduction in the use of radiation for benign disease.

In this case, the intention was not to treat eczema with radiotherapy, but radiation was given postoperatively as adjuvant therapy, and it also resulted in the remission of eczema.

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