Generalized Morphea following Radiotherapy for an Intracranial Tumor
Shrenik Balegar, Dharmendra Kumar Mishra, Sagarka Chatterjee, Shweta Kumari, Anup Kumar Tiwary

Abstract
Morphea is a localized scleroderma variety which can be circumscribed or generalized and is characterized by sclerotic plaques developing on trunk and limbs. Surgery and radiation have been implicated as etiological factors for the development of morphea. Majority of the radiation-induced morphea cases have occurred in patients with breast cancer. The affected areas have been generally restricted to the area of radiation and nearby surrounding area in most of the reported cases. We hereby report a case of a 27-year-old male who developed radiation-induced progressive generalized morphea after getting radiotherapy for an intracranial tumor. His condition improved after dexamethasone-cyclophosphamide pulse therapy. With increased incidence of cancer worldwide and radiotherapy as a modality of treatment, it is imperative to follow the patient and look for the development of morphea which itself is a debilitating disease.

Key Words: Astrocytoma, dexamethasone-cyclophosphamide pulse therapy, en coup de sabre, morphea, seizure disorder

Introduction
Morphea is a chronic autoimmune disease of multifactorial etiology characterized by sclerosis of skin. The etiology and pathogenesis are poorly understood. It arises from a genetic background which increases disease susceptibility combined with other causative factors. Development of morphea is linked to local tissue trauma, surgery, insect bites, intramuscular injections and infections with Borrelia burgdorferi and cytomegalovirus.[1] There is widespread autoimmune reactivity with elevated antinuclear antibodies (ANAs), cytokines, and adhesion molecules.[2,3] Morphea is a rare complication of radiation therapy that has been estimated to occur in 1 in 500 patients.[4] Majority of cases have occurred in patients with breast cancer.[5] The affected areas have generally been restricted to the radiation field or to nearby surrounding area in the majority of previously reported cases. We hereby report a 27-year-old male, who developed generalized progressive morphea after radiotherapy which was given after removal of a benign astrocytoma in his right parietal lobe.

Case Report
A 27-year-old male presented with episodes of headache and seizures since 4 months. Magnetic resonance imaging showed a space occupying lesion in the right frontal lobe [Figure 1]. Local excision of the tumor by craniotomy was done, and tissue sent for histopathological examination. It was found to be a low-grade astrocytoma. Hence, adjuvant radiotherapy was advised by an oncologist. A total dose of 65 Gy were given as external beam radiotherapy. Following irradiation, he developed usual radiation dermatitis and postinflammatory hyperpigmentation which gradually subsided, rather incompletely over 6 months. After 3 months, he noticed linear depressed lesion over the surgical site over forehead and scalp [Figure 2]. Within days, he noticed firm erythematous plaques over back of his thigh, forearms, and trunk which evolved into hyperpigmented atrophic, indurated plaques [Figure 3]. Within 1 year, there was a generalized hardening of skin over abdomen, chest, and forearms leading to limitation...
in mobility of his arms. He could not completely extend his elbow. On examination, there were two linear hyperpigmented depressed scars over forehead showing the classical “en coup de sabre” appearance. The skin was hide-bound and difficult to pinch over both arms and forearms. However, there was no sclerodactyly, Raynaud’s phenomenon, or any other systemic symptoms. Laboratory investigations showed positive ANA but anti-Scl-70, anti-ds-DNA, anticentromere, anti-Ro-La, and anti-topoisomerase antibodies were all negative. His erythrocyte sedimentation rate was 54 mm/h, differential leukocyte count showed eosinophilia (13%). Chest X-ray, computed tomography thorax, and electrocardiogram did not show any abnormalities. A biopsy from the lesion on his lower back showed markedly thickened, hyalinized, closely packed collagen bundles in reticular and papillary dermis [Figure 4a and b]. Sparse perivascular and periappendageal lymphohistiocytic infiltrate, atrophy of pilosebaceous units was seen. There was no mucin deposition. These findings were consistent with morphea, and a diagnosis of radiation-induced generalized morphea was done. Patient was prescribed topical high potent steroids over highly indurated plaques and dexamethasone-cyclophosphamide pulse (DCP) therapy as a systemic treatment for 10 cycles. The plaques softened, generalized hardening, and hyperpigmentation reduced [Figure 5]. Physiotherapy was advised which helped him in regaining joint movement and strength.

Discussion

Morphea is an uncommon cutaneous disorder characterized by circumscribed patches and plaques of sclerotic skin with dermal fibrosis and collagen deposition usually developing on trunk and limbs. It is traditionally classified into circumscribed, linear, bullous, frontoparietal, morphea profunda, and generalized varieties. The etiology is poorly understood and has been linked to local tissue trauma, radiation, surgery, insect bites, and intramuscular injections. Autoimmunity is one of the central features of morphea. Several in vitro studies have shown abnormalities in fibroblasts from patients with morphea. These include fibroblast promotion of migration of mononuclear leukocytes across endothelial cell layer and increased transforming growth factor beta (TGF-β) receptor...
Morphea has been known to occur after bacillus Calmette–Guérin (BCG), Diphtheria-Tetanus-Pertussis (DTP), and measles, mumps, and rubella vaccination following varicella, injections of Vitamin K and B12. Trauma may be a triggering factor and may precede the onset by many months. Surgical trauma has been reported as a stimulus for the development of lesions after arteriovenous fistula formation, rhinoplasty, and laparotomy, and recently mechanical compression from clothing has been suggested to trigger lesions. B. burgdorferi infection is implicated in the etiology of morphea in some studies. Morphea has been reported after therapy with a number of drugs. Cutaneous lesions have also been reported after therapy with bromocriptine, carbidopa, valproic acid, pentazocine, docetaxel, paclitaxel, bleomycin, and after melphalan limb perfusion. Morphea postradiotherapy is a rare complication, with an estimated incidence of 1 in 500 patients in contrast to that of morphea (of any etiology), which is 2.7/100,000 in the general population. Colver et al. Schaffer et al. and Ullén and Björkholm have all reported postirradiation morphea localized to the area of irradiation. Ardern-Jones in 2003 first reported a case of widespread morphea following radiotherapy for carcinoma breast. Recently, Yanaba et al. have reported a case of radiation-induced generalized morphea with prominent mucin deposition. It is rather interesting that in all the above-reported cases, morphea developed following irradiation for breast cancer. It is thought that radiation initiates an initial inflammatory phase followed by “burnt-out” phase characterized by induration, fibroid retraction, and pigmentation. The pathophysiology is thought to be radiation-induced neoantigen formation that subsequently stimulates secretion of TGF-β. TGF-β strongly stimulates fibroblasts, collagen synthesis, and hence excessive fibrosis ensues.

In our case, the irradiation to the brain tumor-induced extensive fibrogenesis elsewhere in the body. Furthermore, he had undergone craniotomy which is also a risk factor for developing morphea. Adding to that, he had high ANA titers which might have contributed to the disease. The prognosis of radiation-induced morphea is good and usually improves with wide variety of treatment modalities such as intralesional or systemic steroids, oral or topical antibiotics, antimalarials, and phototherapy. Recently, calcipotriol has proved beneficial with ultraviolet A1 (UVA)-1. Low-dose broadband UVA as bath or oral photochemotherapy is effective which is thought to result from increased production of collagenase and interferon-δ, decreased TGF-β, and collagen production. Topical tacrolimus and 5% imiquimod has been reported as being beneficial. Numerous systemic agents including phenytoin, p-aminobenzoate, griseofulvin, etretinate, Vitamin E, d-penicillamine, pyridoxine, and cyclosporine have all been tried in open trials for morphea. Physical therapy in the form of physiotherapy is helpful in preventing joint deformities and contractures, and in maintaining joint movement and strength. DCP, a widely acclaimed therapy for autoimmune disorders, is known to soften the morphea lesions with minimal side effects. The progressive and generalized nature of morphea in the patient warranted us to start DCP. Furthermore, it is cheaper and easily available in our center, and the patient responded well.

**Conclusion**

Radiation and surgery are important causative factors for the development of morphea and patients receiving radiotherapy should be followed up for years to detect morphea. The patient had higher titers of ANA. Whether radiation-induced antibody formation or ANAs already present in the patient resulted in morphea is a debatable issue. Considering the number of patients undergoing radiation therapy, morphea following radiotherapy is definitely uncommon. The temporal and presentation pattern of our case does suggest that radiation did trigger morphea. Probably, a subset of patients may be more prone to this complication. We do not know whether all ANA positive patients are prone to morphea and should avoid radiation. DCP therapy can be confidently used in the treatment of generalized morphea.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for
his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

What is new?
Radiation is an important trigger factor of morphea. It not only can induce localised morphea, but also generalised progressive morphea with severe disability. Presence of ANA in a patient increases the susceptibility for developing morphea. Regular monitoring of the patients receiving radiotherapy is recommended.

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