Stevens-Johnson Syndrome in patients receiving cranial irradiation and concomitant diphenylhydantoin

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The routine prophylactic use of anticonvulsants after brain surgery or in patients with brain metastasis without surgery seems to be a variable but common practice, regardless of whether the patient has a previous history of convulsions. Data on the risk of developing adverse drug reactions (ADRs) caused by diphenylhydantoin (DPH) used concomitantly during cranial radiotherapy is still conflicting. Although the exact mechanism is still not well-known, there is increasing anecdotal support in the literature for a synergistic effect between DPH therapy and cranial radiotherapy. Stevens-Johnson Syndrome (SJS) is one of the most severe ADRs which may result with great morbidity and mortality in patients receiving cranial radiation therapy and DPH concomitantly. This report presents 3 cases of this rare syndrome diagnosed in our department in 4 years time. Various authors suggested discontinuation of prophylactic use of anticonvulsants in patients with no history of seizures by emphasizing increased rate of severe mucocutaneous reactions caused by this type of drugs given during radiotherapy, some others have argued in favor of prophylactic anticonvulsants. The risk of seizures reaches 20% to 40% in cases with primary and metastatic brain tumors and the incidence of adverse drug reactions is relatively lower. We believe that the notion rejecting prophylactic anticonvulsant usage in patients with primary or metastatic brain tumors should be evaluated with caution. [Turk J Cancer 2002;32(4):164-171]

Key words: Stevens-Johnson Syndrome, diphenylhydantoin, cranial irradiation, brain metastasis

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous disorders related with more benign form called erythema multiforme, having high rates of morbidity and mortality (1). Both diseases are associated with, episodic acute mucocutaneous hypersensitivity reactions, most of elicited by various drugs and less so by herpes simplex virus
(HSV) and mycoplasma infections, malignancies and collagen vascular diseases (2,3).

SJS is characterized by rapidly expanding purpuric macules and blisters, often by atypical target lesions with prominent involvement of the trunk and face together with more than one mucosal site (oral, pharyngeal, esophageal, conjunctival and anogenital). Although SJS is principally a self-limited disease it may end with sequelae due to mucosal scar formation, or even with mortality.

Mucocutaneous reactions caused by phenytoins and hydantoins are well-known adverse event that occurs through mechanisms yet not completely elucidated. The rate of cutaneous reactions associated with hydantoin is reported to range between 5% and 10% (4). Although rare, it has been emphasized that; there is increased risk of severe mucocutaneous eruptions when anticonvulsants are used in conjunction with radiation therapy, which is a common practice applied for primary and metastatic brain tumors in most of the neurosurgery and oncology clinics (5).

We report three cases of this uncommon dermatological syndrome believed to be due to an interaction between diphenylhydantoin (DPH) and irradiation.

Case 1

A 56-year-old male was admitted to hospital with recent history of occasional transient right arm and facial spasms and accompanying right arm numbness being present for three months. On physical examination he was found to have right hemiparesis (3/5) and right 7th nerve paralysis. During further evaluation a cranial magnetic resonance imaging (MRI) of brain showed a large space occupying cerebral lesion located on the left parietal convexity with 6 cm greatest diameter. Plain chest X-ray showed a large mass located at the upper lobe of the left lung. Bronchial wash was positive with malignant cells and broncoscopic biopsy revealed epidermoid carcinoma of lung. In May 1997 parietal mass was surgically removed. Pathology was reported as brain metastasis from lung carcinoma. In the postoperative period prophylactic dexamethasone (12 mg/day), famotidine (40 mg/day) and diphenylhydantoin (DPH) (300 mg/day) was given. Between May and June 1997 a 44.8 Gy (3.2 Gy/fr) local lung and 21 Gy whole brain external beam radiotherapy was applied consequently. At the sixth day of cranial irradiation, disseminated erythema of both scalp and previously irradiated chest fields has appeared with accompanying conjunctivitis of both eyes. Following day bullous lesions in the same sites, hyperemic patchy lesions of oral mucosa and vesicular lesions of eyelids appeared. Additionally, eye lashes and hairs of involved fields were lost. Laboratory analysis revealed a low leukocyte count with neutrophilic preponderance (leukocyte 2.2 10^9/l, neutrophil count 1.7 10^9/l) and moderately increased transaminases (alanine transaminase: 152 U/l and aspartate transaminase: 103 U/l). There was no detectable eosinophilia and serology was negative for all possible infectious etiology. This clinical findings were characteristic for DPH-radiation induced SJS. Cranial irradiation and DPH were discontinued immediately. After hospitalization, dexamethasone dose was increased up to 24 mg/day and supportive care including i.v. fluids and parenteral nutrition was given. One week later his condition improved gradually and all lesions disappeared leaving highly hyperpigmented fields at involved
sites. Patient was lost due to dissemination of primary site at the seventh month of follow-up.

Case 2

A 44-year-old female patient with a past history of hypertension was admitted to the hospital for evaluation of headache, back pain and pain in both eyes, presenting for five months. Her electrocardiogram (ECG) showed sinus rhythm and left lateral wall ischemia, and plain chest X-ray showed prominent pulmonary conus. She was found to be normotensive with a lipid and cholesterol levels in normal limits. Physical examination revealed mild weakness on the right extremities. As possibility of hypertensive etiology was ruled out, on further evaluation cranial CT showed a solitary right temporoparietal mass with 5 cm greatest diameter. Subtotal surgical excision was performed on September 1998. Pathology was reported as; metastatic neoplasm, predominantly showing malignant melanoma characteristics. Prophylactic dexamethasone (8 mg/day), famotidine (40 mg/day) and DPH (300 mg/day) was given postoperatively. A 30 Gy (3 Gy/fr) whole brain and 15 Gy (3 Gy/fr) local boost field irradiation was planned. On the 10th day of whole brain irradiation she was presented with disseminated facial and periorbital edema accompanied by dysphagia and patchy erythematos lesions of scalp and trunk. Physical examination revealed generalized maculopapular rash with widespread blisters, oral mucosal ulcerative lesions, conjunctivitis and periorbital edema. Laboratory analysis revealed a low leukocyte count with neutrophilic preponderance (leukocyte 2.3 $10^9$/l, neutrophil count 1,9 $10^9$/l) and normal biochemistry. There was no detectable eosinophilia and serology was negative for all possible infectious etiology. Clinical appearance was typical for DPH-radiation induced SJS. Cranial boost radiotherapy was postponed together with immediate DPH discontinuation. After hospitalization the patient was started on i.v. prednisolone 1 mg/kg daily, with i.v. fluids and parenteral nutrition support. A prophylactic broad-spectrum antibiotic with Gram (+) and anaerobic coverage was also administered due to coexisting high fever fluctuating in between 38.3°C and 39.2°C. Her condition gradually improved, all skin and mucosal lesions cleared and the fever subsided. The patient was discharged from the hospital after 11 days and restarted on cranial boost field radiotherapy without any further problems. She died at 9th month of follow-up due to disseminated organ metastasis.

Case 3

A 53-year-old male with previous history of lung carcinoma was admitted to the hospital to evaluate weakness of right extremities existing for 2 weeks. Physical examination revealed right hemiparesis (3/5). On further evaluation, a cranial computerized tomography (CT) showed a solitary mass located on left frontal lobe and a thorax CT showed a mass on the right middle lobe localisation. Gross total excision of left frontal lobe mass was performed on September 2001. Pathology was reported as adenocarcinoma metastasis. Pathological diagnosis was in concordance with pathology of lung primary. Prophylactic dexamethasone (6 mg/day), famotidine (40 mg/day) and DPH
(200 mg/day) was given postoperatively. A 30 Gy (3 Gy/fr) whole brain irradiation was planned. On 26th of October 2001, fifth day of radiation treatment, he was presented with disseminated erythematous lesions of scalp, trunk and both upper extremities. He reported the scalp to be the first site where skin lesions became apparent. Physical examination revealed generalized erythematous maculopapular rash with occasional patchy blisters predominantly involving chest wall and scalp (Figures 1 and 2).

Fig 1. Atypical target lesions presenting on chest wall

Lesions located on upper arms were milder than other sites. There were multiple pinpoint small redden areas on oral mucosa without any sign of ulceration. Laboratory analysis revealed a normal leukocyte count with neutrophilic preponderance (leukocyte 6.3 $10^9$/l, neutrophil count 4.4 $10^9$/l) and normal biochemistry. There was no detectable eosinophilia and serology ruled out all possible infectious etiology including HSV. Clinical presentation was typical for DPH-radiation induced SJS. Rest of radiotherapy was postponed together with immediate DPH discontinuation. Steroid dose was increased to 20 mg/day. Six days later, his condition improved gradually and all lesions disappeared. Radiation therapy was re instituted and applied safely without any further complication and he was on well-being when last seen on 14th of January 2002.
Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are two closely related diseases not yet having precisely established diagnostic boundaries in between. Although it is hard to differentiate one from the other, cases with limited areas of limited detachment are usually labeled SJS and those with extensive detachment as TEN. Dermatologists classify cases with detachment less than 10% of epidermis as SJS and those with more than 30% as TEN. The remaining cases that do not fit in either group are classified as 'overlap syndrome' (6). Both of these clinical syndromes belong to the wide spectrum of drug reactions, ranging from erythema multiforme, which is a self limited eruptive reaction of skin, to the potentially fatal TEN where SJS lies in between (7). Both SJS and TEN can be distinguished from erythema multiforme, which is a more benign form of drug eruption, by presence of atypical flat target lesions. In patients with erythema multiforme target lesions are more typical and are characterized by concentric rings around a central disc (2).

Hydantoin therapy is complicated by cutaneous reactions in 5% to 10% of patients receiving this type of anticonvulsants (4). Although not clear yet, there is substantial evidence suggesting a possible autoimmune process associated with cutaneous diphenylhydantoin reactions leading to multiorgan involvement (8,9). Some recent studies suggest that SJS, TEN and other adverse drug reactions (ADRs) might also have metabolic bases (10). It has been
hypothesized that cutaneous ADRs to sulfonamide and anticonvulsant drugs may be linked to a highly specific defect in detoxification of drug-reactive metabolites. Other suggestions are based on presence of a probable immune mediated mechanism, and many authors have proposed these patients to be treated with immunosuppressive agents (11,12). In one report it has been stated that DPH could cause an immunogenic reaction resembling that of graft-versus-host disease via attaching mononuclear cell membranes (13). No matter whether proposed hypotheses are based on immune or metabolic bases, a genetic susceptibility is suspected: in fact an association between TEN and certain HLA subtypes has been proposed (14).

Radiation as a cause of SJS and TEN has also been described (5,15). Although exact mechanism is not clear yet, in one study radiation has been shown to induce a primary antibody response after an immunization, that may be associated with an impairment of suppressor-T cells (15). Some authors suggested that a disruption of the hypothalamic pituitary axis during cranial irradiation may be the causative factor (16).

The patients presented in this report had constitutional symptoms, atypical skin target lesions, ocular and mucosal involvement on which the clinical diagnosis of radiation-DPH related SJS/TEN was based. Although, there was no histological confirmation; presentation time of the skin and mucosal reactions, clinical characteristics and spreading order of lesions, negativity of viral serology, absence of a strongly accusable second drug and confirmation with dermatology department consultation were all powerful tools supporting our clinical diagnosis of this rare syndrome.

Although not a rule, in general it is believed that ADRs usually develop 2-3 weeks after intake of the offending drug, and it is uncommon for patients to develop these reactions later than a month (1). In our cases, onset of reactions developed at a time when patients had been on anticonvulsant treatment for 5 weeks, making phenytoin alone as a causative agent unlikely. In our view, perhaps it is the combination of radiation, steroids and DPH, each affecting the immune system in its own way to create an environment where the patient is at increased risk of developing SJS or TEN. Majority of cases reported previously show that in cases receiving DPH and cranial irradiation, steroids were also administered (17). In one more recent study steroid usage was reported to delay onset of reactions but having no effect on prevention of disease progression (18).

The routine prophylactic use of anticonvulsants after brain surgery or in patients with brain metastasis without surgery seems to be a variable but common practice. The indication in our cases was just for prophylactic purposes as there was no clear sign or symptom suggesting a history of convulsions. Data on the risk of developing severe ADRs caused by DPH used concomitantly during cranial radiotherapy is still conflicting. However, it has been well established that about 20% of patients with metastatic brain tumors and as many as 40% of patients with primary brain tumors develop seizures during postoperative period or natural course of disease without surgery (15). In a retrospective review it has been stated that only 1 out of 289 patients with brain tumors, who received cranial irradiation and anticonvulsant medications, developed erythema multiforme and this is in parallel with our experience (19). As the incidence of severe mucocutaneous reactions associated with
anticonvulsants and simultaneous irradiation is relatively low, we think that the
notion rejecting prophylactic anticonvulsant usage in patients with primary or
metastatic brain tumors should be evaluated with caution.

Finally, the severity of both SJS and TEN mandates their early recognition
and institution of therapy as soon as possible. This can be possible only by high
levels of physician’s both experience and suspicion. We, therefore, strongly
recommend that the appearance of a skin eruption in the irradiated field of a
patient receiving DPH should be followed closely and, upon sign of
dissemination, both radiation and DPH should be discontinued and high dose
steroids together with supportive care instituted.

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