

Delayed head and neck complications of sulphur mustard poisoning in Iranian veterans

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Abstract

Objective: Sulphur mustard is a chemical warfare agent which was used against Iranian combatants and civilians between 1983 and 1988. The purpose of this study was to document the delayed toxic effects of sulphur mustard in Iranian veterans, focussing on head and neck complications.

Patients and methods: This was a two-year, prospective, descriptive study of 43 male Iranian veterans aged 34 to 48 years (mean 41.8 years) who were moderately disabled or worse due to sulphur mustard poisoning. Investigations were performed with consent, including haematological, biochemical and immunological tests, spirometry, chest X-ray, high resolution computed tomography of the lungs, and skin biopsies. Further investigations and interventions were performed as clinically indicated.

Results: The most affected sites were the lungs (95 per cent), peripheral nerves (77 per cent), skin (73 per cent), eyes (68 per cent), and head and neck (16.2 per cent). Of seven patients with mostly head and neck complications, four had a skin disorder (hyperpigmentation in all four, an erythematous, papular rash in two, and dry skin in one). Two patients had thyroid cancer (undifferentiated thyroid carcinoma in one and papillary carcinoma of a thyroglossal cyst in the other, 12 and 14 years after sulphur mustard exposure, respectively). One patient had nasopharyngeal carcinoma, 12 years after sulphur mustard exposure.

Conclusion: Carcinomas of the thyroid and nasopharynx in three patients with sulphur mustard exposure are reported for the first time.

Key words: Chemical Warfare Agent; Sulphur Mustard; Thyroglossal Cyst; Cancer; Head And Neck

Introduction

Sulphur mustard is a chemical warfare agent which was widely used during World War I and by Iraqi forces against Iranian combatants and even civilians between 1983 and 1988.^{1–3} Sulphur mustard is regarded as one of the most important agents of chemical warfare; its simple, cheap chemical synthesis makes it readily available for both military and terrorist use. Sulphur mustard is an alkylating agent that induces disruption of nucleic acids and proteins, impairing cell homeostasis and eventually causing cell death.^{4–6} The widespread use of sulphur mustard as an incapacitating chemical warfare agent in the past century has revealed its long-lasting, highly toxic effects. This knowledge may lead to further use of sulphur mustard in future military conflicts and terrorist attacks.

Sulphur mustard exerts its toxicity through a number of postulated pathogenic mechanisms, including deoxyribonucleic acid alkylation, DNA depletion and glutathione inactivation.^{7,8} The eyes, skin and respiratory system are the three major targets for the direct toxic effects of sulphur

mustard. When absorbed in large amounts, the substance can produce further, systemic toxicity, damaging the proliferating cells of the bone marrow and other organs, which may result in both short- and long-term impairment of the organs.^{9–16}

There have been several publications on the early and delayed toxic effects of sulphur mustard.^{1–16} A wide range of delayed toxic effects has been reported, including chronic bronchitis, bronchiectasis, frequent bronchopneumonia and pulmonary fibrosis, all tending to worsen with time.^{17,19–21} The most distressing long-term consequences of sulphur mustard exposure include severe dry skin, delayed keratitis, and a pathogenic status of cell-mediated immunity with subsequent increased risk of infection.²⁰ There have also been reports of malignancy associated with sulphur mustard poisoning.^{22–25} However, there is no information in the literature about the delayed toxic effects of sulphur mustard in the head and neck.

The current study was undertaken to investigate the delayed toxic effects of sulphur mustard in the head and neck region, in Iranian veterans.

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Materials and methods

The 2004 report of the Khorasan Veteran Foundation listed 1845 chemically injured veterans in the Iranian province of Khorasan. The chemical warfare agents confirmed to have been used during the Iraq–Iran war were sulphur mustard, sarin and Tabun. After obtaining the approval of the Azad Medical University medical ethics committee, the medical files of the poisoned veterans were reviewed and summarised on pre-designed forms. The Iranian Veteran’s Foundation Medical Committee, an expert medical committee, had evaluated the severity of late complications in these patients and classified them as normal, mild (i.e. grade one), moderate (grade two) severe (grade three) and very severe (grade four). Since sulphur mustard (SM) is a blistering agent, severity grading based on the skin complication that the expert committee had recommended, was used in this article to show the severity of SM complication (Table 1). Based on the extent of complications in various organs, Grade 2 was considered as mild intoxication (0–25% disability), Grade 3, as moderate (25–50%), Grade 4 as severe (50–70%) and Grade 5 as very severe (>70%).

TABLE I
GRADING OF SKIN COMPLICATION SEVERITY IN SUBJECTS WITH
SULPHUR MUSTARD POISONING*

Diagnostic category		Findings
Grade	Description	
1	No specific complications	No objective signs or symptoms
2	Mild skin complications	Hyper- or hypopigmentation, atrophy, hypertrophy, poikiloderma & dry skin, involving 1–18% of skin surface area
3	Moderate skin complications	Hyper- or hypopigmentation, atrophy, hypertrophy, poikiloderma & dry skin, involving 19–36% of skin surface area
4	Severe skin complications	Hyper- or hypopigmentation, atrophy, hypertrophy, poikiloderma & dry skin, involving >36% of skin surface area

Wallace’s ‘rule of nines’ was used to estimate percentage of burned skin surface area. *Classification of the Iranian Veteran Foundation’s Medical Committee

An invitation to participate in the study was extended to all non-smoking veterans who had been exposed to sulphur mustard (60 patients) and who had: more than 50 per cent disability due to sulphur mustard poisoning; no history of exposure to any other chemical warfare agent; and no other chronic disease. Following explanation of the study, 43 patients (aged 34 to 48 years) gave written, informed consent to participate. These individuals were studied between 2004 and 2006. They underwent clinical and paraclinical investigations performed by specialised staff, including ultrasonography and computed tomography. Results were recorded on pre-designed forms. Invasive interventions such as skin biopsy and surgery were undertaken as clinically indicated. Following ethical consideration, the first author performed standard surgical procedures. Pathological examinations were performed by the third author, with results being confirmed by a more experienced pathologist.

Results

All patients were male, with a mean age of 41.8 years. The most affected sites were the lungs (95 per cent), peripheral nerves (77 per cent), skin (73 per cent), eyes (68 per cent), and head and neck region (16.2 per cent). Seven patients had significant head and neck manifestations. Four of these had skin complications, as presented in Table II. The results of skin biopsy in two of these four patients are presented in Table III.

Thyroid cancer was diagnosed in two patients.

The first patient was diagnosed with undifferentiated thyroid carcinoma, 12 years after exposure to sulphur mustard. He died 10 days after surgery (total thyroidectomy and bilateral radical neck dissection) due to carotid blow-out.

The second patient developed papillary carcinoma of a thyroglossal cyst, 14 years after sulphur mustard exposure.³² This patient, a 36-year-old man, presented with a midline neck nodule, three months before admission into hospital. Ultrasonography revealed cystic lesions measuring 38 and 16 mm above the thyroid gland. Thyroid function and fine needle aspiration examination of the thyroid were normal. A Sistrunk procedure was performed. Macroscopic examination revealed two cysts fused by connective tissue and hyoid bone. The cysts showed a fibrous wall lined by respiratory epithelium, with normal areas of thyroid tissue located in the wall. A focal, projecting area of papillary cell carcinoma was seen, with fibromuscular stroma covered by a single or double

TABLE II
DELAYED HEAD AND NECK SKIN MANIFESTATIONS IN PATIENTS WITH SULPHUR MUSTARD POISONING

Pt no	Age (yr)	Presentation delay* (yr)	HP	Atrophy	Dryness	CA	Eczema	Lesion grade	Disability (%)	Biopsy
1	38	17	+	+	–	+	–	4	40	+
2	38	17	+	–	+	–	–	2	70	–
3	38	17	+	+	–	–	–	4	50	+
4	46	20	+	–	–	–	+	2	40	–

*Time interval between exposure and presentation. Pt no = patient number; yr = years; HP = hyperpigmentation; CA = cherry angioma; += present; – = absent

TABLE III
CLINICOPATHOLOGICAL FINDINGS FOR SKIN LESIONS OF PATIENTS 1 AND 3

Pt no	Biopsy site	Clinical presentation	Pathological findings
1	Right arm	Atrophic, hyperpigmented scar	Atrophy of epidermis, hyperkeratosis, basal layer hyperpigmentation, severe dermal fibrosis & adnexal atrophy
3	Lower back	Atrophic, hyperpigmented scar	Hyperkeratosis, basal layer hyperpigmentation, dermal fibrosis, & scattered & perivascular lymphocyte infiltration

Pt no = patient number

layer of cuboidal cells with 'ground glass' nuclei and psammoma bodies. Total thyroidectomy with lymph node sampling was performed. Microscopic examination of the surgical specimen showed multifocal papillary carcinoma in the isthmus and both thyroid lobes. The lymph node contained papillary cell carcinoma metastasis. The patient was given ablative radioactive iodine treatment and thyroid suppression with levothyroxine. He survived, and his final thyroid scan in December 2006 was normal.

Nasopharyngeal carcinoma (NPC) was diagnosed in another patient, 12 years after sulphur mustard exposure. This patient complained only of a headache initially, but after six months he developed unilateral serous otitis media due to NPC. At the time of diagnosis (one year after the onset of symptoms), the patient had extensive, intracranial tumour extension. He died three months after receiving radiotherapy.

A summary of the three patients presenting with cancer of the head and neck is given in Table IV.

Discussion

Based on our long-term experience, it would appear that the toxic effects of sulphur mustard persist in the human body, and that relapse or new disease can occur many years after exposure.^{12–22} It must be emphasised that effects of this kind result from a single dose or brief exposure to sulphur mustard, and differ from those caused by chronic poisoning, which requires further exposure.²⁴ The term 'late complications of sulphur mustard poisoning' has been used to refer to all organ dysfunction and abnormality occurring several years after initial exposure.^{12–29}

The first report on the Iranian veterans suffering from Nitrogen Mustards and on the delayed toxicity of sulphur mustard poisoning in 236 Iranian veterans found that effects were most common in the respiratory tract (78 per cent), central nervous system (45 per cent), skin (41 per cent) and eyes (36 per cent).⁸ These effects were recorded between two months and 28 months after exposure. The patients were all followed from the early phase of sulphur mustard poisoning, and included cases of mild to severe toxicity. In another study, of 34 000 Iranians exposed to sulphur mustard, complications were found most commonly in the lungs (42.5 per cent), eyes (39.5 per cent) and skin (24.5 per cent).²⁹ There were some similarities and differences between the two studies. The differences may be due to the fact that most of the latter study's cases involved only mild sulphur mustard exposure, whereas the former study included only severe cases of sulphur mustard poisoning and undertook its investigations 18–23 years after initial exposure.

On the basis of laboratory studies, sulphur mustard is classified as a carcinogen. Human studies have indicated a causal association between occupational exposure to sulphur mustard and the excessive occurrence of respiratory cancer, skin cancer and leukemia.²⁴ Investigation of former workers at a sulphur mustard plant from 1929 to 1945 found significant excess mortality due to respiratory cancer (33 cases observed versus 0.9 expected) and a highly significant excess of laryngeal cancer.^{30,31} A study of former employees of a British plant that manufactured sulphur mustard noted cases of cancer of the pharynx and other upper respiratory sites, as well as a moderate, but still very significant, excess mortality

TABLE IV
PATIENTS PRESENTING WITH HEAD AND NECK CANCER, 16–20 YEARS AFTER SULPHUR MUSTARD EXPOSURE

Age (yr)	Presentation delay* (yr)	Cancer site	Diagnosis [†]	Therapy	Outcome
34	12	Thyroid	Undifferentiated Ca	Total thyroidectomy Bilateral radical neck dissection	Death due to carotid blow-out 10 days post-op
36	14	Thyroglossal duct cyst & thyroid	Papillary Ca	Sistrunk procedure	Alive without disease
38	12	Nasopharynx	Nasopharyngeal Ca	Total thyroidectomy with lymph node sampling Radiotherapy	December 2006 Death 3 months post-radiotherapy

*Time interval between exposure and presentation. [†]Confirmed by histopathology. Yr = years; Ca = carcinoma; post-op = post-operative

from lung cancer.²⁴ Gastric cancer, basal cell carcinoma, Bowen's disease and skin spinocellular carcinoma have all been reported following occupational exposure to mustard gas.^{24,30,31}

Patients with thyroglossal duct cyst malignancy are at high risk of thyroid malignancy if they received low-dose neck irradiation in childhood or if they have a thyroglossal duct cyst carcinoma larger than 1.5 cm.³² In our patient with papillary carcinoma within a thyroglossal cyst, due to sulphur mustard exposure, total thyroidectomy and lymph node resection were performed despite a normal thyroid examination and a negative thyroid scan, because we believed that this patient was at high risk of thyroid malignancy (based on the laboratory classification of sulphur mustard as a carcinogen). Histopathological examination of the surgical specimen revealed multifocal papillary carcinoma of the thyroid with metastasis to at least one cervical lymph node.³²

- Sulphur mustard is a chemical warfare agent which was widely used during the First World War and by Iraqi forces against Iranian combatants and civilians between 1983 and 1988
- Sulphur mustard has a wide range of delayed toxic effects, including chronic bronchitis, bronchiectasis, frequent bronchopneumonia and pulmonary fibrosis, all of which tend to worsen with time
- This was a two-year, prospective, descriptive study of 43 male Iranian veterans who were more than 40 per cent disabled due to sulphur mustard poisoning
- Three patients had carcinoma of the thyroid or nasopharynx; this effect is reported for the first time

Based on the results of our study, we believe that long-term follow up and further investigation and monitoring of sulphur mustard exposed veterans are required to protect their health and also to learn more about the delayed toxic effects of this chemical warfare agent.

Conclusion

We report, for the first time, the appearance of carcinomas of the thyroid and nasopharynx in three patients exposed many years previously to sulphur mustard as a chemical warfare agent. Veterans exposed to sulphur mustard require further follow up and investigation in order to protect their health and also to learn more about the delayed toxic effects of this chemical warfare agent.

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