

CASE REPORT

Formaldehyde-induced urticarial vasculitis

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SUMMARY

A 40-year-old male medical student presented with urticarial vasculitis secondary to occupational formaldehyde exposure. Serum sickness and delayed pressure urticaria also featured prominently during his illness. Initial symptom control was achieved with oral prednisolone (25 mg/day tapered to zero over 2 weeks) and oral antihistamine therapy (fexofenadine 180 mg once daily, promethazine 20 mg once daily, ranitidine 150 mg twice daily); however, subsequent exposures to formaldehyde produced transient symptom flares that broke through the prednisolone cover. A complete recovery occurred only after strict elimination of all exposure to formaldehyde, both occupationally and in the home environment, was achieved.

Key words: delayed pressure urticaria, immune complex disease, medical education, occupational exposure, serum sickness.

INTRODUCTION

The aetiology of urticarial vasculitis is not well understood, and in the majority of cases, the cause is deemed to be idiopathic.¹ Infrequently, a trigger for a patient's illness is found, and systemic lupus erythematosus, Sjögren's syndrome, the use of certain medications and viral infections have all been documented.¹ Chemical exposure has rarely been reported to cause urticarial vasculitis, and we report a presentation of this condition in a medical student that was secondary to occupational formaldehyde exposure.

CASE REPORT

A 40-year-old male medical student presented with a 2-week history (Fig. 1) of an erythematous rash, covering

his scalp, trunk, arms and legs. The patient reported 50–100 lesions daily. Systemic manifestations included arthralgia, myalgia, constipation, dyspepsia and painful swallowing.

The lesions were characterized by central clearing, a burning sensation that accompanied pruritus, duration between 24 and 48 hours, and a residual transient hyperpigmentation. Histology of an urticarial lesion of 24 hours' duration biopsied from the dorsum of the left foot was consistent with urticarial vasculitis. There was a perivascular lymphocytic infiltrate, neutrophils and eosinophils within oedematous blood vessel walls and leukocytoclasia. Immunofluorescence stains were negative for features of systemic lupus erythematosus.

Initial symptom control was achieved with oral prednisolone (25 mg/day tapered to zero over 2 weeks) and a combination of oral H₁ and H₂ antihistamines (fexofenadine 180 mg once daily, promethazine 20 mg once daily, ranitidine 150 mg twice daily). Within 24 hours of prednisolone completion, the patient developed a serum sickness reaction, consisting of fever, rigors, arthralgia and a return of urticarial lesions. Oral prednisolone therapy was restarted with a prolonged taper (25 mg/day tapered to zero over 4 weeks).

Two weeks later, the patient experienced bronchoconstriction during an anatomy dissection course. The course involved the dissection of cadavers preserved with formaldehyde, and the patient had commenced dissection activities 7 weeks prior to initial presentation. Formaldehyde concentrations in the anatomy dissection laboratory are monitored, and time-weighted average exposures have been measured at just less than 1000 parts per billion, with peak exposures up to 2000 parts per billion. The patient was exposed to these concentrations of formaldehyde twice weekly for 2 hours per session. He was instructed to immediately withdraw from the course.

The patient had changed to a formaldehyde-containing laundry detergent 2 months prior to initial presentation. The concentration of formaldehyde in the laundry detergent was reported to not exceed one part per thousand. The patient was instructed to stop using this detergent and to change to a formaldehyde-free product.

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Abbreviation:

F-HSA formaldehyde–human serum albumin

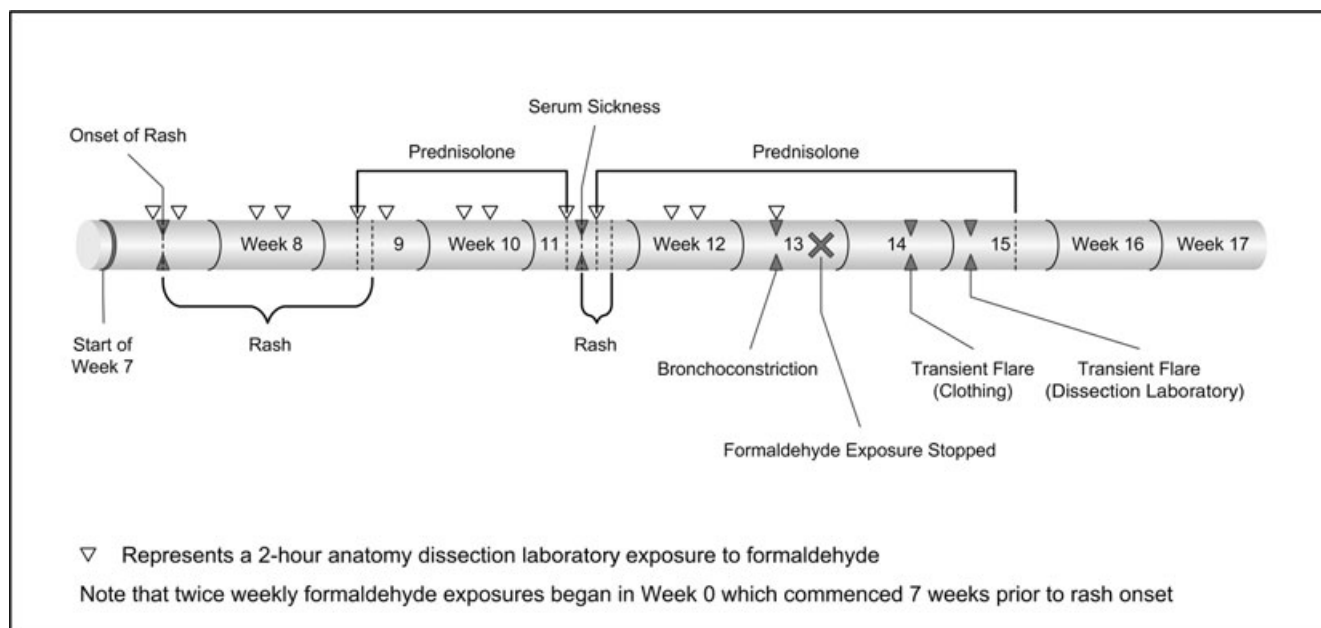


Figure 1 Clinical Timeline.

Table 1 Laboratory test results

Abnormal results investigation	Reference range	Initial workup	Recovery
Total protein	65–80 g/L	79	83
Lactate dehydrogenase	115–200 U/L	248	218
C-reactive protein	<8 mg/L	35	11
Erythrocyte sedimentation rate	2–12 mm/hour	29	

Negative titres: *Helicobacter pylori*, hepatitis B and C, cytomegalovirus, HIV, Epstein–Barr virus

Normal results: full blood examination, electrolytes, urea, creatinine, bilirubin, liver enzymes, albumin, globulins, immunoglobulin A, immunoglobulin E, complement components 3 and 4, Anti DNA B antibody, antistreptolysin-O titre, rheumatoid factor, antigliadin antibody, antinuclear antibody, extractable nuclear antigen antibody, anti-double-stranded DNA antibody, antineutrophil cytoplasmic antibody, thyroxine, thyroid-stimulating hormone, antithyroid microsomal antibody

The second prednisolone taper was completed 17 days later, at which point the vasculitic lesions did not return. The patient did, however, begin to experience mild delayed pressure urticaria with between one and five lesions presenting daily. These lesions were restricted to pressure points and did not leave residual hyperpigmentation. The delayed pressure urticaria gradually regressed, requiring increasing pressure to induce a wheal, and resolved completely 4 months later.

As the second course of prednisolone was tapered, occasional transient urticarial flares broke through the prednisolone cover and were attributed to formaldehyde exposures. These exposures included voluntarily returning to the dissection laboratory for an important teaching session, wearing permanent press fabrics which contain formaldehyde releasers, and inhaling turboprop exhaust while accompanying a medivac flight.

The patient's medical history was significant for mild seasonal allergic rhinitis and infrequent upper respiratory tract infections, the most recent of which resolved 3 months prior

to the current presentation. The patient was not on any medication for 2 months prior to symptom onset.

Laboratory test results are shown in Table 1. In addition, a T.R.U.E Test® allergen patch test series was performed to detect a Type IV hypersensitivity to formaldehyde. This test was negative for formaldehyde, and no contact urticarial lesions were noted.

DISCUSSION

Formaldehyde is a ubiquitous compound, and exposures to elevated concentrations are associated with occupational fumes, building materials, permanent press fabrics, cosmetics, household cleansers and cigarette smoke.² Environmental concentrations of formaldehyde vary between 0.8 and 16 parts per billion.³ Our patient was exposed to levels two orders of magnitude greater, and given that an episode of bronchoconstriction occurred concurrent with an exposure, the potential for formaldehyde hypersensitivity had to be considered.

The investigations performed excluded all known aetiologies for urticarial vasculitis. Of greatest diagnostic significance was the patient's recovery after measures to limit formaldehyde exposure were implemented. Once formaldehyde exposures were curtailed, the patient's vasculitis resolved, and both C-reactive protein and lactate dehydrogenase declined substantially towards normal. The transient urticarial flares following subsequent unplanned challenges to formaldehyde further support an association between formaldehyde exposure and this patient's urticarial vasculitis.

The timing of the patient's serum sickness reaction also supports formaldehyde hypersensitivity. The episode of serum sickness that followed the first prednisolone course implies that an environment of antigen excess existed at this point in time. Prednisolone therapy would have restricted antibody production over the prior 2 weeks, and the patient's formaldehyde exposure on the day prednisolone therapy was completed is a notable source of excess antigen. To contrast, a serum sickness reaction did not occur when the second course of prednisolone was completed at a time when formaldehyde exposure had been curtailed.

Both urticarial vasculitis and serum sickness are Type III hypersensitivity reactions. Even though contact urticarial lesions were not observed, the patch test was conducted to rule out the more common association of formaldehyde exposure to allergic contact dermatitis, a Type IV hypersensitivity reaction. It is important to stress that the negative patch test result only rules out allergic contact dermatitis and cannot be interpreted to either support or discount a Type III reaction.

Formaldehyde is metabolized primarily by glutathione-dependent formaldehyde dehydrogenase.⁴ The clearance of formaldehyde is rapid, with a half-life in plasma of only 1 min.⁴ Prior to elimination, formaldehyde has the opportunity to conjugate with a single protein, to cross-link two proteins, or to form protein–DNA cross links.⁵ Formaldehyde-altered proteins can be immunogenic by formaldehyde either behaving as a hapten⁵ or inducing a conformational change in the host protein.⁶

An hypothesized mechanism for formaldehyde-induced urticarial vasculitis is shown in Figure 2. Formaldehyde frequently binds albumin to form a F-HSA conjugate.⁷ This F-HSA conjugate is capable of triggering production of immunoglobulin-G antibodies.⁵ Alternatively, a hapten such as formaldehyde may conjugate with any protein for which it has high affinity, and this haptenated protein or one of its metabolites may be antigenic.⁸ Exposures below a threshold are likely insufficient to trigger an immune response allowing basal environmental levels of formaldehyde to be tolerated. However, as formaldehyde levels approach 75 parts per billion, increased immune activation against formaldehyde has been detected.⁹

An association between contact urticaria syndrome, delayed pressure urticaria and formaldehyde hypersensitivity has previously been reported in the literature.¹⁰ In addition, Type III hypersensitivity reactions to formaldehyde have been reported manifesting as membranous nephritis.¹¹

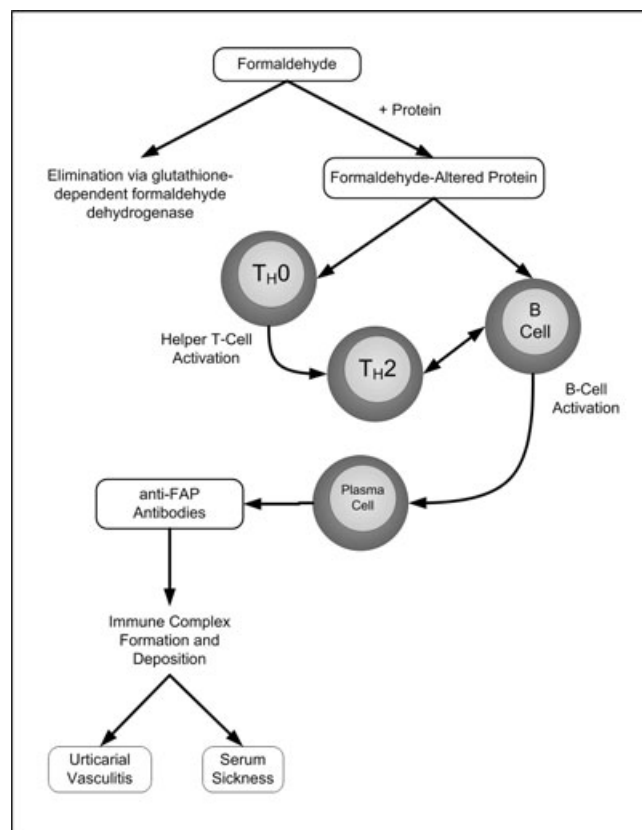


Figure 2 Proposed Mechanism of Action for Formaldehyde Induced Urticarial Vasculitis.

The strong clinical association of symptoms to occupational formaldehyde exposure in this case supports a diagnosis of urticarial vasculitis, serum sickness and delayed pressure urticaria secondary to formaldehyde hypersensitivity.

In conclusion, the publication of this case report endeavours to improve the recognition of pathologies that may be induced by formaldehyde. Successful treatment of formaldehyde-induced urticarial vasculitis is directly dependent on combining appropriate pharmacotherapy with strict measures to limit the patient's exposure to formaldehyde both occupationally and in the home environment.

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