ALLERGIES IN THE WORKPLACE

OCCUPATIONAL VITILIGO IN ASSOCIATION WITH AUSTRALIAN BLACKWOOD DUST AS A NOVEL RISK FACTOR

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ABSTRACT

Occupational vitiligo is an acquired depigmenting disorder of the skin that can be caused by certain chemical skin exposures in the workplace in genetically susceptible people. The association between vitiligo and occupational chemical exposures was first described in 1939 in leatherworkers in relation to exposure to mono-benzyl ether of hydroquinone in rubber gloves. Since then an increasingly long list of chemical agents, and in particular the phenol/catechol derivatives, have been associated with the development of vitiligo. Our understanding of the complex interplay of genetic and environmental risk factors has been improved through the recent discovery of NALP1 and certain other genes implicated in conferring susceptibility to vitiligo and other autoimmune and autoinflammatory conditions. This article looks at a sentinel case of occupational vitiligo instigated by contact with Australian blackwood (*Acacia melanoxylon*) dust in a cabinet maker, with good resolution of lesions following his removal from exposure and treatment.

Introduction

Vitiligo is an acquired depigmenting disorder of the skin due to decreased or absent melanin, and histological examination reveals either complete or partial loss of melanocytes from the epidermis.[1-3] Vitiligo occurs with a frequency that ranges from 0.1% to 2.0% in various populations, with clustering in families suggestive of a multifactorial polygenic inheritance pattern.[4]

Although not life-threatening, vitiligo can cause considerable disability because of a change in the physical appearance of the skin, as well as physical discomfort during the acute inflammatory stage when there may be pruritus and irritation and from sunburn of the depigmented lesions. Vitiligo is associated with an extended phenotype of autoimmune and autoinflammatory conditions such as Hashimoto's thyroiditis, Grave's disease, type 1 insulin-dependent diabetes mellitus, Addison's disease, autoimmune polyendocrinopathy syndrome, systemic lupus erythematosus, pernicious anaemia and inflammatory bowel disease.[4-6] Alkhateeb *et al.*[4] reported that autoimmune thyroid disease was about eight times more frequent in people with vitiligo as compared with the general population. This suggests a common gene defect conferring susceptibility to both vitiligo and other autoimmune and autoinflammatory conditions.[7]

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Vitiligo was previously classified as idiopathic; however recent research has provided insight into the complex relationship between various genetic and environmental risk factors that leads to the development of this disease.[8-10]

There are many chemicals known to trigger vitiligo in susceptible people. This paper examines occupational exposure to Australian blackwood (Fig. 1) dust and reveals it as a novel risk factor for occupational vitiligo in the setting of genetic susceptibility. The wood's botanical name *Acacia melanoxylon* is ironic. '*Melanoxylon*' comes from the Greek root, *melanos*, the same root as for the affected cell, the melanocyte. *Melanos* means 'black', but perversely the wood caused the skin to turn white instead of black.

Fig. 1. Australian blackwood (Acacia melanoxylon).

Case report

A 42-year-old man who works as a solid-wood cabinet maker developed an itchy depigmenting rash which lasted for 4 years preceding the diagnosis of occupational vitiligo. The development of the rash coincided with a significant worsening of his control of asthma. The rash started shortly after he had compled his training as a cabinet maker and commenced employment at a local joinery company that manufactures solid-wood furniture. The rash and itching seemed to get worse when he used certain woods and in particular when Australian blackwood (*Acacia melanoxylon*) was used. Significantly the rash improved when he went on holiday and worsened when he recommenced work. It started initially as itchy red papules with scaling, in a patchy distribution over the face, limbs and body. It was particularly evident around the wrist and under the watchstrap, on the forearms, elbow flexures, axillae, lower back especially in the midline, umbilicus, and around the neck, chin and mid-face. Gradually the areas became depigmented. The depigmented lesions would slowly recover over weeks to months, especially with the use of clobetasol proprionate 0.05% cream, prescribed by a local doctor. Repigmentation would start from within the lesion as small brown macules around the hair follicles and would then slowly expand outwards. On the dorsum of the fingers, distal to the middle phalangeal joint, the lesions would repigment partially and only from the edge of the lesion.

He also developed work-related deterioration in his asthma control in association with exposure to certain hardwood dusts, in particular African rosewood (*Pterocarpus erinaceus*). He developed shortness of breath, a cough and wheezing, sometimes within 15 minutes of exposure to African rosewood dust, and symptoms frequently lasted into the night. This was associated with monthly exacerbations requiring oral corticosteroids, and in June 2007 he was started back on an inhaled corticosteroid (budesonide 200 µg daily) by his local doctor.

Before changing his career to become a cabinet maker and while training at a local technical college, he had had no skin problems and his asthma was well controlled without the need to use inhaled corticosteroids. During training he did not work with expensive hardwoods and used mainly pine. Effective dust extraction ventilation was employed in the training workshops. He was otherwise well with no other medical conditions.

A workplace visit was conducted to assess exposures. Hardwood was supplied from a sawmill in the southern Cape, which was treated with Lindane at the sawmill before being air-dried for about a year. The dried hardwood from the mill was cut to the correct thickness and edged before being laminated with glue if required for making table tops. The wood was then further sanded with an electric sander, and cut before being assembled by the cabinet maker as the required piece of furniture. The assembled piece was then given a finishing sanding before being sprayed or varnished. Spraying of the furniture with various coatings was performed in an enclosed room with extraction ventilation. The cabinet maker worked only on the assembly of the piece and was not involved in varnishing or applying sealants or paints to the wood. Apart from the spraying booth, the rest of the process occurred in a large factory space with very poor extraction ventilation and excessive levels of wood dust visible to the naked eye. The wood exposures identified were SA pine (*Pinus*), oak (*Quercus*), Oregon pine, maple, Australian blackwood, African rosewood, yellow-wood (*Podocarpus falcatus*) and cottonwood. Other exposures included wood glue, the rubber handles of tools, metal screws and soaps, all of which were not thought to be significant exposures because the distribution of the rash suggested airborne allergens.

Figures 2 and 3 show the typical appearance of depigmented patches with focal areas of repigmentation around the hair follicles. The watchstrap area and neck, chin and area around the nose are particularly affected; this is due to accumulation of dust on the collar, in the beard, under the watchstrap and where the face mask makes contact with the skin.

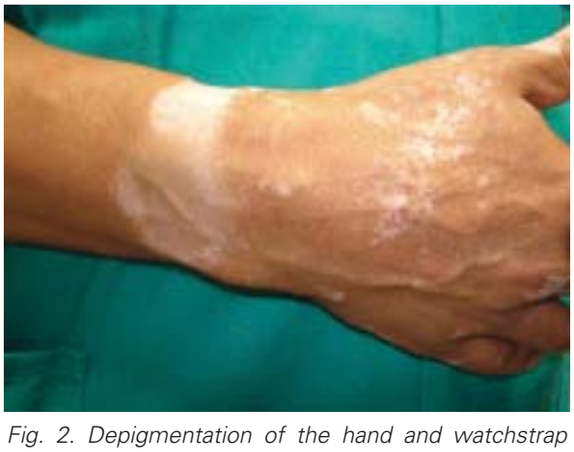

Fig. 2. Depigmentation of the hand and watchstrap area.

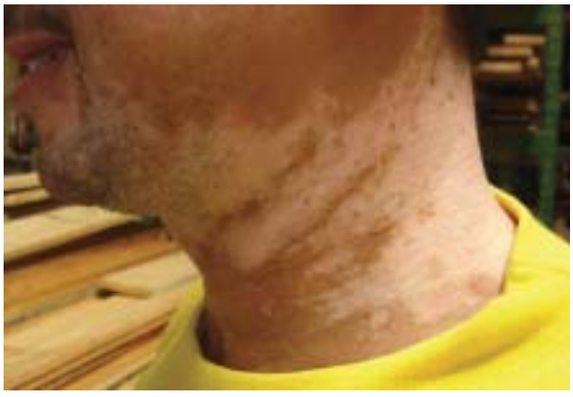

Fig. 3. Depigmentation of the chin, beard and neck area.

A spongiotic dermatitis with pigmentary incontinence was shown on histology (Fig. 4). An autoimmune screen confirmed that he was antinucleotide-factor- and anti-double-stranded-DNA-negative. In addition his thyroid stimulating hormone, full blood count, erythrocyte sedimentation rate, liver functions, creatinine and glycosylated haemoglobin were all within normal limits. His total IgE was 387 IU (>100 IU). A skin-prick test to common aeroallergens was positive for a wide range of aeroallergens, confirming that he was atopic. A patch test to wood dusts showed a 1+ positive reaction to Australian blackwood and a negative reaction to African rosewood, cottonwood, yellow-wood, Oregon pine and oak. The standard battery patch test to 43 allergens was 2+ positive to nickel sulphate.

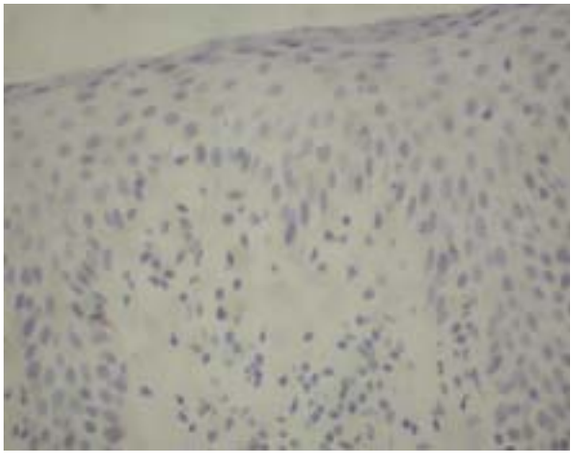

Fig. 4. Melan A immunochemical stain. Absence of stainable melanocytes in the basal epidermis is in keeping with the diagnosis of vitiligo.

On the basis of the work-related history, typical appearance, histopathology results and positive patch test to *Acacia melanoxylon,* the diagnosis of occupational dermatitis and vitiligo was made. The Lindane that was used to treat the wood was not considered a significant exposure as all the hardwood supplied from the sawmill was treated with Lindane, yet the worker's reaction was confined to exposure to Australian blackwood and African rosewood. He was treated with topical corticosteroids, initially using the potent topical corticosteroid clobetasol proprionate 0.05% with weaning to less potent creams once the inflammation had subsided. At the same time psolaren and UVA (PUVA) treatment was started. He was also advised to stop working with the *Acacia* and *Pterocarpus* family of woods and given education on hand care.

His asthma was further investigated and treated with inhaled corticosteroids and inhaled beta-adrenergic

agents. His case was notified to the Department of Labour as a potentially compensable case of occupational dermatitis and work-aggravated asthma.

He elected to resign from the company and to start his own business specialising mainly in pine furniture. He did however continue to work with hardwoods but never worked with either African rosewood or Australian blackwood. Over the next 6 months he made steady progress with no further occurrences and the depigmented areas gradually repigmented. In some lesions the repigmentation was partial while in other lesions complete repigmentation was achieved (Fig. 5).

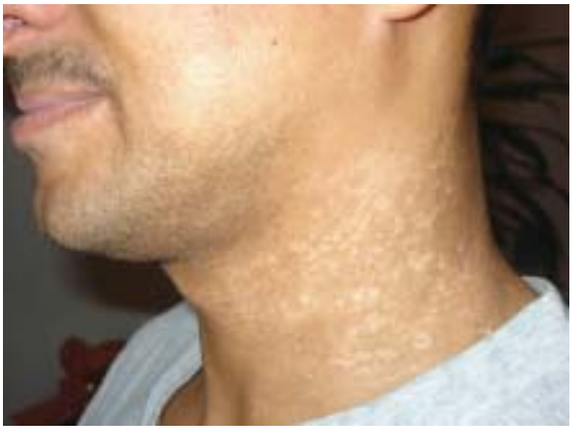

Fig. 5. Repigmentation after discontinuation of exposure and treatment.

Discussion

Over the last few years, the pieces in the 'vitiligo puzzle' have started to 'fall into place'[9] especially with the recent identification of the NALP1 gene.[8]

The complex environmental and genetic risk factors for vitiligo are now thought to revolve around the melanocyte proteins – tyrosinase [9] and tyrosinase-related protein-1(TRP-1)[10] and their interaction with the immune system and exogenous compounds. Genetic susceptibility is thought to be conferred by: (i) a variety of single nucleotide polymorphisms in and around the NALP1 gene that code for proteins involved in the innate immune system, in particular the T cells and Langerhans cells involved in skin autoimmunity;[8] and (ii) other genes associated with vitiligo such as the VIT1, catalase, tenascin and FOXD3 genes which are either involved in repressing immune response, combating oxidative stress, repairing DNA or maintaining melanocytes on the basement membrane or facilitating melanocyte migration.[10]

The biochemical mechanisms leading to vitiligo seem to involve in concert or as isolated events: (i) a build-up of hydrogen peroxide from oxidative stress that results in excess production of o-quinones by the melanocyte enzyme tyrosinase; (ii) an excess of catecholamine-like molecules that are also converted by tyrosinase to o-quinones; (iii) an altered redox state that promotes excess o-quinones production through reduced cycling; (iv) exogenous chemicals particularly phenolic and catechol derivatives[10] that are oxidatively converted to o-quinones in the epidermis or may be directly toxic to melanocytes.

Current thinking is that o-quinones link with tyrosinase to form a hapten complex that is then seen as non-self by the innate immune system in susceptible people, triggering an autoimmune response that leads to destruction of melanocytes through activated T cells and Langerhans cells.[9] Tyrosinase is involved in the production of the pigment melanin from the substrate tyrosine and if the enzyme is not functioning properly this could lead to impaired pigment production. Furthermore there is also some evidence that the humoral immunity may also be involved in melanocyte destruction through autoantibodies in certain people.[5] TRP-1 is thought to mediate the cytotoxicity of phenol/catechol derivates with mutant TRP-1 genes conferring susceptibility to these compounds.[9,10]

Since 1939 when occupational exposure to rubber gloves, containing mono-benzyl ether of hydroquinone was first associated with vitiligo of the hands and forearms in leather workers,[11] an increasingly long list of chemicals has now been linked to occupational vitiligo. In the early 1970s, the link between paratertiary butyl phenols used as adhesives in the manufacturing of tyres and resins was associated with vitiligo and systemic effects.[12] Boissy and Manga in 2004[10] published a list adapted from Miyamoto and Taylor[13] of agents currently thought to trigger occupational vitiligo in susceptible people.[10] This list has been adapted slightly for this article with the addition of *Acacia melanoxylon* (Table I).

To date there has only been one other report found that associates exposure to wood products with the development of vitiligo. Kumar and Freeman[14] in 1999 reported a case of vitiligo in a worker exposed to pine wood and colophony in the form of medium-density fibre (MDF) particle board.[14] It is not certain whether it was the wood or chemicals used in the production of the particle board that was responsible for the vitiligo.

Various wood dusts have been associated with the development of occupational asthma, with the American Conference of Governmental Industrial Hygienists (ACGIH) in 2005 listing 90 different species of softwood, tropical-wood and hardwood dusts known to be allergenic and associated with occupational asthma. Included in this list is Australian blackwood. African rosewood is not included in the list. Australian blackwood is associated with lower and upper respiratory tract symptoms as well as allergic contact dermatitis,[15-17] and De Zotti and Gubian[18] in 1996 reported *Acacia* dust exposure in association with asthma.[18] The immune mechanisms in allergic contact dermatitis and allergic occupational asthma are different, with contact dermatitis being a delayed-type immune reaction and allergic occupational asthma due to a type 1 IgE-mediated immune response (although in some cases a poorly understood non-IgE-mediated response is found, especially with low-molecular-weight molecules that act as haptens in triggering an immune reaction).

A number of different chemicals have been isolated from Australian blackwood that act as sensitisers resulting in allergic contact dermatitis or asthma in susceptible people. Naturally occurring quinones such as 2,6-dimethoxy-1,4-benzoquinone and acamelin have been isolated and shown to be sensitisers,[19-22] and more recently hydroxyflavans have been isolated from Australian blackwood and shown to be allergenic.[23] The author postulates that either naturally occurring quinones or possibly hydroxyflavans in the Australian blackwood dust triggered vitiligo in this susceptible patient.

In our patient good resolution of the vitiligenous lesions was evident once the exogenous trigger was removed and treatment with topical corticosteroids and PUVA started.

Identification of *Acacia melanoxylon* as a cause of occupational vitiligo is important as it provides authorities with additional evidence for adjudication of compensation for this worker and for future workers who

Table I. Materials and agents associated with contact/occupational vitiligo

Materials containing phenol/catechol derivatives	**Other non phenol/catechol derivative chemical agents**
Germicidal detergents	*Sulfhydryls*
Disinfectants	b-Mercaptoethylaminehydrochloride (cysteamine)
Varnish and lacquer resins	N-(2-mercaptoethyl)-dimethylaminehydrochloride
Synthetic oils	Cystaminedihydrochloride
Duplicating paper	Sulfanolicacid
Plasticizers	3-Mercaptopropylaminehydrochloride
Insecticides	
Printing inks	*Miscellaneous*
Paints	Mercurials
Photographic chemicals	Arsenic
Rubber antioxidants	Cinnamic aldehyde
Motor oil additives	p-Pheylenediamine
Deodorants	Benzylalcohol
De-emulsifiers for oil field use	Azaleicacid
Latex gloves	Corticosteroids
Soap antioxidants	Optic preparations
Formaldehyde resins	Eserine(physostigmine)
Adhesives	Diisopropylfluorophoshate
Valve plants	Tio-tepa(N,N¢,N¢¢-triethylene-thiophosphoramide)
	Guanonitrofuracin
	Systemic medications
	Chloroquine
	Fluphenazine (prolixin)
	Wood dust – *Acacia melanoxylon* (new agent from this paper)

Adapted from Boissy and Manga.[10]

may develop occupational vitiligo from wood-dust exposure. PUVA treatment is expensive and successful adjudication in favour of the worker allows for compensation of costs for PUVA treatment in South Africa in terms of section 4.3 of circular instruction 181 from the COID Act No. 131 of 1993.

Medical practitioners should be aware that Australian blackwood, which is commonly used in the manufacturing of hardwood furniture and musical instruments, as well as a range of other chemical agents, is an occupational risk factor for vitiligo. Furthermore, medical practioners should also be aware that various wood dusts are risk factors for work-related asthma and contact dermatitis. Workers who present with these conditions and are exposed to one of these agents may be eligible for compensation. Investigation at a specialised unit may be required in order to perform punch biopsy, patch testing or further investigation for work-related asthma.

Declaration of conflict of interest

The author declares no conflict of interest.

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