The immunological role of the skin as target organ in occupational lung diseases

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Background

• Occupational lung diseases such as isocyanate asthma and chronic beryllium disease continue to occur despite reduced airborne exposures.
• Although challenging to quantify, recent studies have documented isocyanate and beryllium skin exposure, even with the use of personal protective clothing.
Background

• Animal studies demonstrate that skin exposure to isocyanates and protein allergens is highly effective at inducing sensitization, with subsequent inhalation challenge eliciting asthmatic responses.
Background (2)

Generally, occupational exposures to the traditional inorganic dusts such as asbestos, silica and coal dust were reduced.

But there is an expanding use of new metal chemical-based products which induces predominantly immune-mediated occupational lung diseases in most developed countries.
Immunology Background

Isocyanate asthma
• TH2 type
• Type I Hypersensitivity Reaction

Chronic beryllium disease
• TH1 type
• Type IV Hypersensitivity Reaction
Immunology Background

Isocyanate asthma
TH2 type
Type I Hypersensitivity
Isocyanate aerosol in the respiratory tract leads to binding of isocyanate to tubulin, impaired cilia function, and detachment of bronchial epithelia cells. Free, unbound isocyanate can conjugate with albumin (Hapten-Carrier-Complex), forming isocyanate-albumin complex; neo-antigen. Induction of an immune response by dendritic cells involves uptake of the complex by antigen-presenting cells (APC), presentation of antigen on MHC II, activation of T-cells, and cytokine production. CD4+ T-cells can activate cytotoxic immune response via CD8+ CTLs and Th2 cells that secrete IL-4 and IL-9 leading to Th2 cell activation and IL-13 production. B-cells are involved in the formation of IgE-AB, which is part of a humoral immune response. Detoxification of bound isocyanate occurs through binding to reduced glutathionones, catalyzed by glutathione-S transferase, systemic diversion of the glutathione-isocyanate complex.
Figure 1. Mechanisms Involved in Sensitizer-Induced Asthma and Irritant-Induced Asthma.

High-molecular-weight (HMW) agents act as complete antigens and induce the production of specific IgE antibodies, whereas the low-molecular-weight (LMW) agents to which workers are exposed that induce specific IgE antibodies probably act as haptens and bind with proteins to form functional antigens. Histamine, prostaglandins, and cysteinyl leukotrienes are released by mast cells after IgE cross-bridging by the antigen. After antigen presentation by dendritic cells, T lymphocytes can differentiate into several subtypes of effector cells. Antigen-activated CD4+ cells can differentiate into cells with distinct functional properties conferred by the pattern of cytokines they secrete. Type 1 helper T (Th1) cells produce interferon-γ and interleukin-2. Type 2 helper T (Th2) cells release cytokines such as interleukin-4, -5, and -13; activate B cells; and promote IgE synthesis, recruitment of mast cells, and eosinophilia. CD8+ cells also release interleukin-2 and interferon-γ and correlate with increased disease severity and eosinophilic inflammation. Innate natural killer cells may also release interleukin-13 in response to products of cell damage. There is evidence that some LMW agents, such as diisocyanates, can stimulate human innate immune responses by up-regulating the immune pattern-recognition receptor of monocytes and increasing chemokines that regulate monocyte and macrophage trafficking (e.g., macrophage migration inhibitory factor and monocyte chemoattractant protein 1). Further interleukin release includes interleukin-1 and -15. Injury to the airway epithelium is likely to play a central role in the pathogenesis of irritant-induced asthma. Oxidative stress is likely to be one of the mechanisms causing the epithelial damage. Inhalation of irritants is likely to induce the release of reactive oxygen species by the epithelium. Furthermore, there may be an increased release of neuropeptides from the neuronal terminals, leading to neurogenic inflammation with release of substance P and neurokinins.
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Immunology Background

Chronic Beryllium Disease

TH1 type

Type IV Hypersensitivity
Immunologic Reaction to Be++
a Primary immune surveillance

- Lymph node
- Injury/pathogen
- Activated mature dendritic cells bearing antigen migrate to local lymph node
- Naive T cells recirculate through local lymph node seeking antigen
- Blood vessel

b Secondary immune surveillance

- Antigen non-specific recruitment of CLA^+ effector memory T cells primed in skin-draining lymph node

C Tertiary immune surveillance

- Dendritic cells in other tissues, such as the lungs, gut, and muscle, take up antigen and migrate to local draining lymph nodes
- Lymph node
- TCR, CLA, MHC, CCR7
- Central memory T cells recirculate through local lymph node seeking antigen from respective tissue
- Blood vessel
Isocyanate asthma and skin exposure

- Numerous obstacles make it difficult for epidemiologic studies to more rigorously assess whether skin exposure contributes to asthma risk. Most importantly, methods to sample and quantitate skin exposures generally are not well developed or widely available, unlike airborne exposure methods.

- Determination of dermal exposure - field sampling and work-up procedure MDI monomers on the skin of 24 workers is measured using the tape-strip technique

- Tape-strip sampling for measuring dermal exposure to 1,6-hexamethylene diisocyanate. Scand J Work Environ Health. 2006

- Quantification and statistical modeling--part II: dermal concentrations of monomeric and polymeric 1,6-hexamethylene diisocyanate. Fent KW, Ann Occup Hyg. 2009

Isocyanate asthma and skin exposure


- Dermal and inhalation exposure to methylene bisphenyl isocyanate (MDI) in iron foundry workers. Liljelind I. Ann Occup Hyg. 2010


- Dermal, inhalation, and internal exposure to 1,6-HDI and its oligomers in car body repair shop workers and industrial spray painters. Pronk A. Occup Environ Med. 2006
Recent findings: Occupational lung diseases such as isocyanate asthma and chronic beryllium disease continue to occur despite reduced airborne exposures.

Although challenging to quantify, recent studies have documented isocyanate and beryllium skin exposure.

Factors that impair skin barrier function, such as trauma, may promote sensitization to such agents.
Immunology Background

Chronic Beryllium Disease
TH2 type
Type IV Hypersensitivity
Health Effects of Beryllium

Routes of Exposure

Health Effects

- **Lungs**
  - Acute beryllium disease
  - Lung cancer
  - Beryllium sensitization (BeS)
  - Chronic beryllium disease (CBD)

- **Skin**
  - Several skin effects
  - BeS
BERYLLIUM SKIN NODULES

Cutaneous nodules can develop, especially if beryllium has penetrated the skin. These nodules tend to be located on exposed areas of skin, such as fingers and forearms.
Because a clear relationship between airborne beryllium level and risk of BeS and CBD has not been established, other routes (e.g., dermal) and/or factors may be important in determining sensitization to beryllium.
Chest wall shrapnel-induced beryllium-sensitization and associated pulmonary disease


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ABSTRACT. Chronic beryllium disease (CBD) is an exposure-related granulomatous disease mimicking sarcoidosis. Beryllium exposure-associated disease occurs mainly via inhalation, but skin may also be a source of sensitization. A 65-year-old male with a history of war-related shrapnel wounds was initially diagnosed with pulmonary sarcoidosis. Twenty years later, the possibility of a metal-related etiology for the lung disease was raised. A beryllium lymphocyte proliferation test, elemental analysis of removed shrapnel, and genetic studies were consistent with a diagnosis of CBD. This case demonstrates that retained beryllium-containing foreign bodies can be linked to a pathophysiologic response in the lung consistent with CBD. (Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 147-150)

KEY WORDS: beryllium sensitization, shrapnel, chest wall

A 41-year-old non-smoking male was referred due to persistent dyspnea and non-productive cough. Thirty years previously, serving as a paramedic in the Suez Canal in the 1973 Yom Kippur War, he experienced a traumatic injury from an 81
A non-smoking male was initially referred to our clinic in 1986 at age 41 for evaluation of persistent dyspnea and non-productive cough.

Thirteen years previously, while serving as a paramedic in the Suez-Canal in the 1973 War, he had experienced a war-related traumatic injury from an 81 mm mortar shell explosion.

His injuries included retained shrapnel in the chest wall, some of which had been surgically removed early in post-wound follow-up.
• At the time of his initial evaluation at our clinic in 1986, his physical examination was unremarkable except for a few small scars in chest wall due to the prior war injuries.

• Radiographic evaluation, including computerized tomography (CT) demonstrated bilateral hilar and mediastinal lymphoadenopathy, and confirmed the presence of retained metallic shrapnel in his right chest wall.
CASE REPORT -3

- Pulmonary function testing TLC 79%, DLco/VA; 78%.
- The patient underwent a further diagnostic evaluation for suspected sarcoidosis.
- The TBB at the time of bronchoscopy was nondiagnostic.
- This included BAL that demonstrated a lymphocytosis (27%) and a CD4/CD8 ratio of 2.6.
- The Kveim-Siltzbach test was positive and gallium scanning yielded findings consistent with sarcoidosis.
- A presumptive diagnosis of sarcoidosis stage I was made.
- The patient’s symptoms improved without gluccorticosteroid treatment and yearly clinic visits revealed no worsening of symptoms.
- His body burden of shrapnel was not considered in his differential diagnosis at that time.
Twenty years later (2006), he was invited to take part in a clinical trial involving sarcoidosis.

Repeat CT imaging demonstrated improvement of the lymphoadenopathy and no appreciable parenchymal involvement.

Follow-up measurement of the DLco/VA, however, demonstrated a fall to 65% of predicted and the TLC was 90% of predicted.
CASE REPORT -5

• At this point, it was raised the possibility of a link between his retained shrapnel and sarcoidosis.
• The possibility of CBD mimicking sarcoidosis was considered because beryllium may be present in military hardware.
• His occupational history was noncontributory: he was an office worker since military discharge.
• Fortuitously, he had been given and kept fragments of shrapnel that had been surgically removed years before.
RESULTS

• The present work-up considered:
• A beryllium lymphocyte proliferation test (BeLPT).
• Genetic evaluation for susceptibility for beryllium sensitization.
• Scanning Electron microscopy (SEM) of the shrapnel.
• The original biopsy specimen was not available for re-review.
The BeLPT yielded a positive test (SI above the normal value of 2.5) with BeSO₄ after 4-6 days of incubation (100 µM=4.1-7.6; 10 µM =3.3-25.3; 1 µM=1.76- 23, respectively) suggesting a strong sensitization with specific reactivity to beryllium.
Genetic study

• In order to assess whether the patient fell into one of the known increased risk genetic groups for CBD, we carried out genotyping for HLA-DPB1.

• This analysis demonstrated heterozygosity with 0201(Glu69+)/0402(Glu69-) alleles, consistent with genetic susceptibility to CBD (Done by L. Maier et al National Jewish Denver Co USA)
FIGURE 2. Schematic risk estimation of individuals with typical allele combinations in their HLA-DPB1 and DPA1 genes commonly seen in CBD (left two) and in controls or in the total population (right two). All filled symbols represent HLA-DPA1 genes and their protein products, α-chains, while all open symbols represent HLA-DPB1 genes and their protein products, β-chains. The p values in columns 1, 2, and 4 were corrected for four different HLA-DPB1 haplotype categories.
RESULTS-2

(Done in University Syracuse, NY by Jerrold Abraham et al).

• In light of the positive BeLPT, we wished to analyze samples of the patient’s shrapnel.

• **SEM** of the samples showed that the major contents were aluminum (Al) and brass (copper and zinc), with multiple other elements at lower concentrations, but not beryllium!
Hi Lizi
You probably thought I had forgotten, but I had not had access to the SIMS analysis instrument until a couple of days ago. and we were able to document Beryllium in the aluminum shrapnel fragment!!
the detected Be was in very small fragments within the Aluminum metal .. also many other bits of interesting things were identified too..
Secondary Ion Mass Spectrometry (SIMS) is a highly specialized analytical tool which combines high spatial resolution and high sensitivity.
Since SEM/EDS does not have enough sensitivity for beryllium detection, we used SIMS further analysis for the detection of beryllium. SIMS can detect ppm to ppb concentrations of beryllium, which is ideal for this type of examination of the shrapnel fragments. The SIMS analysis confirmed traces of beryllium in the matrix of the predominantly aluminum shrapnel fragment.
Discussion

• We present here the first reported case of war-wound shrapnel-induced CBD.
• As is common with CBD, the patient had long since been misdiagnosed as having sarcoidosis.
Discussion-2

• This case also raises intriguing questions regarding **non-inhalational** triggers of beryllium-related disease.

• **Skin** contact, in general, has gained increased attention as a potential route of initial sensitization in what is later manifest as immunological **occupational lung disease**.

• **Skin** contact is believed to be a potential route for systemic sensitization for beryllium as well.
Skin as a Route of Exposure and Sensitization in Chronic Beryllium Disease

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Chronic beryllium disease is an occupational lung disease that begins as a cell-mediated immune response to beryllium. Although respiratory and engineering controls have significantly decreased occupational beryllium exposures over the last decade, the rate of beryllium sensitization has not declined. We hypothesized that skin exposure to beryllium particles would provide an alternative route for sensitization to this metal. We employed optical scanning laser confocal microscopy and size-selected fluorospheres to demonstrate that 0.5- and 1.0-μm particles, in conjunction with motion, as at the wrist, penetrate the stratum corneum of human skin and reach the epidermis and, occasionally, the dermis. The cutaneous immune response to chemical sensitizers is initiated in the skin, matures in the local lymph node (LN), and releases hapten-specific T cells into the peripheral blood. Topical application of beryllium to C3H mice generated beryllium-specific sensitization that was documented by peripheral blood and LN beryllium lymphocyte proliferation tests (BeLPT) and by changes in LN T-cell activation markers, increased expression of CD44, and decreased CD62L. In a sensitization–challenge treatment paradigm, epicutaneous beryllium increased murine ear thickness following chemical challenge. These data are consistent with development of a hapten-specific, cell-mediated immune response following topical application of beryllium and suggest a mechanistic link between the persistent rate of beryllium worker sensitization and skin exposure to fine and ultrafine beryllium particles. Key words: beryllium, exposure, particle, sensitization, skin.

Flow cytometric analysis was performed 48 hr after challenge.

A protracted dissolution half-life to provide a concentration of beryllium in the epidermis also evaluated 0.5-, 2-, and 4-μm spheres. We

Figure 1. Confocal microscopic imaging of human skin. (A) Following the flexing procedure (see “Materials and Methods” for details), optical scans were obtained at 1-μm intervals through a 20-μm-thick tissue section. (B) A three-dimensional image of the cross section of tissue shown in (A) reconstructed by Voxelview software, version 2.5.4 (Vital Images Inc., Minneapolis, MN) from the optical scans obtained for each sample. (C) Data were obtained from the center of the tissue section as designated by the yellow arrow.
Conclusions

• To this limited literature, we now add this case of shrapnel-induced beryllium sensitization with CBD.

• We raise the question as to whether other cases of CBD due to similar exposures have occurred and have been misdiagnosed as sarcoidosis.

• At the very least, patients with retained shrapnel and a clinical presentation consistent with sarcoidosis should be assessed for beryllium sensitization.
ראسيدים
של חקוקה

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הנורה: קביעת דרגת נכס - בדיקת חותם - תקונה 9


קבעה כי יש לקו עין תכלות את המאורת ברוביו על ר. חותם המוברעת לפי תקונה 9.

הועדה קבעה את דרגת נכס לפי הפירות המбуд:

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<td>תחומי התכנון</td>
<td>הערצות אוזן לאל תיפסקים</td>
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</tbody>
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דרגת נכסותkok
דרגת נכסות kok ינשא בהכרח קביעה ר PropertyValue 10.03.2011

הנה להトップות להעתה או תכנית 03.09.2011 45鸬 משלב ב-
היתרורים פגמן קביעה.
Conclusions

• Recent developments collectively support a greater focus on the role of skin exposure in promoting sensitization and the development of asthma and other primarily immune-mediated lung diseases caused by occupational and environmental exposures.

• If such exposures contribute to disease, workplace exposure monitoring practices that focus exclusively on airborne exposures may falsely indicate ‘safe’ exposure levels.

• There are sufficient data, however, to conclude that it is prudent to attempt to minimize both skin and inhalation workplace exposures.
thank you