Berylliosis as an Auto-Immune Disorder

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ABSTRACT

Exposure to compounds of beryllium can cause dermatitis, acute pneumonitis and chronic pulmonary granulomatosis (“berylliosis”) in humans. These syndromes seem to have an allergic-immunologic component in common. Hypersensitivity to beryllium is of the delayed (cell-mediated) type and can be measured as skin reactivity to patch test; lymphocyte blast transformation; and macrophage migration inhibition. There is good correlation between the results of these tests in exposed populations, but the degree of hypersensitivity is not necessarily a measure of either extent of exposure or severity of berylliosis. In animal experiment, inhalation exposure has suppressed a previously established cutaneous hypersensitivity, and degree of hypersensitivity and degree of berylliosis were in significant inverse correlation.

Introduction

Beryllium is a light metal widely used in fatigue-resistant alloys, nuclear reactors, space vehicle and missile parts, electronics and for other specialized purposes. Exposure to compounds of beryllium has caused dermatitis, acute pneumonitis and chronic pulmonary granulomatosis (“berylliosis”) in humans. The dermatitis is of the allergic type with edematous lesions following contact with soluble salts or with granulomatous ulceration following the cutaneous imbedding of insoluble compounds. Acute pneumonitis followed inhalation of soluble salts in high concentration; typical attacks resolved with complete recovery within several months. The chronic granulomatosis is an insidious and slowly developing disease with considerable mortality. It is associated with inhalation of various, including insoluble, beryllium compounds, sometimes in very low concentration. Occupational as well as “neighborhood” cases (the latter having occurred in the general population living within about a mile from a beryllium plant) are on record; they are collected in a “Beryllium Case Registry.”

The allergic nature of beryllium skin lesions was recognized by Curtis, who developed a patch test. Concurrently, Sterner and Eisenbud noted that the epidemiology of chronic pulmonary berylliosis cases also suggested an allergic etiology. Specifically, it was noted by them that a dose-response relation between exposure and incidence was emphatically absent, with workers from the
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cleanest plants and neighborhood cases sometimes showing the worst clinical forms. Furthermore, the morphology of pulmonary granulomata caused by beryllium, with considerable similarity to those observed in sarcoidosis, also allowed the assumption of an immunological etiology. The lesions typically consisted of a cluster of monocytes surrounded by a zone of lymphocytes and plasma cells.36 These findings created the impression that cutaneous and pulmonary beryllium lesions may be interrelated, and pulmonary berylliosis may be in some way dependent on immune reactions in the organism.

Search for humoral antibodies was made24,27,35 and some increases in serum β- and γ-globulin fractions were noted. However, these turned out to be essentially nonspecific. In 1959, it was pointed out that the skin reaction to beryllium being delayed, the immunity is likely to be cell-mediated.37 Alekseeva1 and Cirla et al6 accomplished passive transfer of hypersensitivity in guinea pigs with lymphoid cells, while the transfer of serum was ineffective. Chiappino et al4,5 were also able to inhibit all cutaneous reactions to beryllium in guinea pigs by injection of an antilymphocyte serum from rabbits. Turk and Polak31 could suppress reactivity by intravenous injection of beryllium lactate. Inhalation exposure to beryllium sulfate could also suppress cutaneous reactivity.26 Among guinea pigs, not all individuals responded identically to the beryllium challenge. Ability to become sensitized was genetically controlled and transmitted as a non-sex-linked, dominant trait.23

Mode of administration and choice of beryllium compound also influenced the nature of the immunological reaction. Vacher32 found only those forms and routes which were capable of producing a complex with skin constituents as immunogenic; freely diffusible forms were “tolerogenic”, including a very low dose of beryllium intraperitoneally or a high toxic dose intravenously. Krivanek and Reeves18 showed that the beryllium ion acted as a hapten in provoking the immunological reaction. Complexes where the beryllium ion was unavailable (aurintricarboxylate, citrate) could not elicit sensitivity, whereas beryllium serum albuminate could elicit stronger sensitivity than the beryllium ion alone. Vasil’eva33,34 detected beryllium-nucleoprotein complexes which were antigenic. However, evidence was also presented that beryllium can interact with cells without prior complexing to macromolecules and can inhibit the response of allergized lymphocytes to antigen.15,16

These results strongly suggested that the pathogenesis of beryllium disease contained an immunologic component. The application of this component for purposes of diagnosis was further explored by Epstein and collaborators12-14 who first performed lymphocyte blast transformation and macrophage migration inhibition in preparations originating from beryllium-sensitive subjects.

Patch Test

The earliest diagnostic use of immunologic phenomena in berylliosis was the Curtis patch test.8 All of the 13 beryllium dermatitis cases reacted positively to beryllium fluoride. Eight to ten cases also reacted positively to beryllium chloride, nitrate or sulfate. Only three reacted positively to beryllium metal powder and none to beryllium oxide powder. However, application of the test appeared to be itself sensitizing and eight out of 16 controls who have never been previously exposed to beryllium compounds experienced spontaneous flareup or eczematous reactions at the test site. In 1955, Sneddon26 reported that a patient with positive patch test to beryllium developed a sarcoid-like granuloma at the
test site. Even though Curtis later9 extended his observations to 32 chronic pulmonary berylliosis cases, all of whom reacted positively to the patch test (with 19 out of 21 control patients reacting negatively) it was obvious that extreme caution was advisable in the application of this measure.7,11,20,37,38

Lymphocyte Blast Transformation

Lymphocyte blast transformation can be defined as the morphological enlargement of small lymphocytes to large lymphoblasts in vitro.21 The transformation can be brought about by numerous stimuli including tissue antigens, specific antigens, antisera and a group of very active stimulants referred to as "nonspecific" of which phytohemagglutinin is the prototype. In 1970, Hanifin et al.12 showed that among specific antigens, beryllium compounds (including the insoluble oxide) caused striking transformation of lymphocytes from beryllium-sensitive subjects only, while the lymphocytes from normal, nonsensitive subjects did not transform. Transformation of beryllium-sensitive and nonsensitive lymphocytes by phytohemagglutinin was similar. In 1973, Deodhar et al.10 reported on the exploitation of this discovery for the diagnosis of berylliosis. Among 35 patients with chronic berylliosis, 25 (71 percent) showed at least some blast transformation (with 21 patients showing strong or very strong transformation), even though these patients were treated at the time of the test with prednisone, an inhibitor of immune reactions. There was also correlation between the severity of the clinical disease and the degree of blast transformation. Incidence of positive results in control groups was low: two out of 28 beryllium workers without the disease; three out of 19 normal healthy subjects; and one out of 11 patients with other lung diseases.

Macrophage Migration Inhibition

Bloom and Bennett5 in 1966 demonstrated a soluble factor which could inhibit the free migration of macrophages in vitro. The factor was elaborated by sensitized lymphocytes and appeared to be highly antigen-specific but not cell- or species-specific. It appeared possible to culture pure populations of lymphocytes from buffy coat in the presence of an antigen and then test the supernatant of such a culture on guinea pig peritoneal exudate cells. Inhibition of migration of the latter cells was observed if, and only if, the source of lymphocytes was a sensitized patient. This principle was successfully employed with beryllium as antigen by Henderson et al.14 who demonstrated that beryllium oxide-stimulated lymphocytes from patients with berylliosis, but not from normal individuals, produced the inhibitory factor. Marx and Burrell19 studied seven patients with chronic beryllium disease by means of the macrophage migration inhibition test and found positive results in all, while the results in six normal controls and two non-berylliologic pulmonary patients were negative. On the other hand, Jones-Williams17 examined seven other chronic berylliosis patients and found positive results only in one—but the latter patients were on corticosteroid therapy at the time of testing. It thus seems that macrophage migration inhibition is also a useful indicator of beryllium hypersensitivity although it can be abolished by immunosuppressive treatment.

Correlation of Test Results

Krivanek and Reeves18 as well as Palazzolo and Reeves22 have recently examined the correlation of the aforementioned methods of assaying delayed hypersensitivity to beryllium in animal experimentation. In a population of guinea pigs, frequency distribution of
Figure 1. Frequency distribution of the 24-hour response diameter for control and injected guinea pigs skin tested with intradermal BeSO₄ (0.1 ml of 5 percent solution).

Skin reaction diameters 24 hrs after intradermal injection of 1 y Be (as SO₄) showed about 3.5 mm as the threshold of a significant immunologic reaction (figure 1). This intensity of reaction corresponded to about 20 percent migration inhibition of peritoneal exudate cells (figure 2). Skin reaction diameters and percent migration of the macrophages gave a correlation coefficient of -0.45 (figure 3). The correlation of skin reaction diameters and percent blast transformations has thus far not been quantified but is also believed to show definite interdependence.¹⁰,¹⁴

Correlation of Hypersensitivity to Pulmonary Berylliosis

Pulmonary berylliosis can be produced experimentally in guinea pigs by inhalation exposure to beryllium sulfate.²⁵ If the exposed animals were previously sensitized by intradermal beryllium sulfate injections, it was found that inhalation exposure suppressed cutaneous hypersensitivity (figure 4).

The degree of pulmonary berylliosis acquired by these animals can be quantified as lung weight-body weight (LW/BW) ratios because lung weights in pulmonary berylliosis, as in most other pathologic conditions of the lung, tend to increase while body weights stay stationary or, in severely sick animals, decrease. In uninjected animals, LW/BW ratios showed good dependence on both the length and concentration of beryllium exposure. In intradermally sensitized animals, the LW/BW ratios increased less, and there was negative correlation between LW/BW ratios and skin reaction diameters (figure 5) or between LW/BW ratios and macrophage migration inhibition (figure 6).
Discussion

Skin testing, lymphocyte blast transformation and macrophage migration inhibition are methods of assessing delayed hypersensitivity to an allergen. All three methods appear suitable to demonstrate the state of hypersensitivity to beryllium, but since skin testing is an in vivo procedure believed to cause itself sensitization occasionally, it is best not used on human patients. Among the two in vitro tests of lymphocyte blast transformation and macrophage migration inhibition, it is the latter that has received more intensive quantitative study thus far although both appear suitable measures of delayed hypersensitivity to beryllium.

It should be emphasized that these tests measure a state of hypersensitivity to beryllium, not a state of berylliosis. The two conditions may or may not go hand-in-hand in exposed humans. In experimental guinea pigs, a reverse correlation was shown to exist. Beryllium inhalation suppressed an already established cutaneous hypersensitivity and pathologic response to beryllium inhalation was milder in sensitized than in nonsensitized animals. Inhalation exposure is naturally attended in some measure by trace ingestion of the disseminated compound. This can have an immunosuppressive effect. As for the apparent immunity to pulmonary berylliosis conferred by intradermal treatments, the situation shows some similarity to the relation of tuberculin sensitivity to tuberculosis, where also a controlled induction of sensitivity (e.g., with BCG vaccine) is associated with increased resistance to tuberculosis. Perhaps the lymphocytic and histiocytic response that follows the induction of cutaneous hypersensitivity stimulates the phagocytosis of inhaled beryllium particles or otherwise helps to destroy the auto-antigen formed in the lungs.
Conclusions

Beryllium is an allergen capable of inducing delayed cutaneous hypersensitivity. Beryllium inhalation causes granulomatous disease of the lungs, the development of which apparently depends on immune mechanisms. The degree of hypersensitivity can be measured by patch testing, lymphocyte blast transformation or macrophage migration inhibition.

In some but not all cases of human berylliosis, cutaneous hypersensitivity accompanies the lung disease. It must be emphasized that the afore-mentioned tests are diagnostic for beryllium hypersensitivity, not for berylliosis. In animal experiment, degree of hypersensitivity and degree of berylliosis showed an inverse correlation.

References